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# Application of Organolithium and Related Reagents in Synthesis. Part 22[1]. Synthetic Strategies Based on Ortho-Aromatic Metallation. A Concise Regiospecific Conversion of Benzoic Acids into the 4-Pyridyl-2H-Phthalazin-1-Ones

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# APPLICATION OF ORGANOLITHIUM AND RELATED REAGENTS IN SYNTHESIS. PART 22[1]. SYNTHETIC STRATEGIES BASED ON *ORTHO*-AROMATIC METALLATION. A CONCISE REGIOSPECIFIC CONVERSION OF BENZOIC ACIDS INTO THE 4-PYRIDYL-2*H*-PHTHALAZIN-1-ONES.

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**Abstract**: The synthesis of phthalazin-1-ones **6**, **7**, **8** via the reaction of 3-hydroxyisoindolin-1-ones **3**, **4**, **5** with hydrazine hydrate is described. Starting compounds **3**, **4**, **5** were regiospecifically prepared upon the lithiation (*n*-BuLi) of the benzanilides **1** and subsequently the reaction of the dilithiated anilides **2** with methyl pyridinecarboxylates.



It has been shown, recently, that some 2,4-disubstituted 2*H*-phthalazin-1-one derivatives, for example such as 2-ethyl- or 2-(1-imidazolyl)ethyl-4-(3-pyridyl)-2*H*-phthalazin-1-one **B** [R = H, $R^1$ = Et or 2-(1-imidazolyl), Py = 3-*pyridyl*], have both thromboxane $A_2$ ($TXA_2$) synthetase inhibitory and

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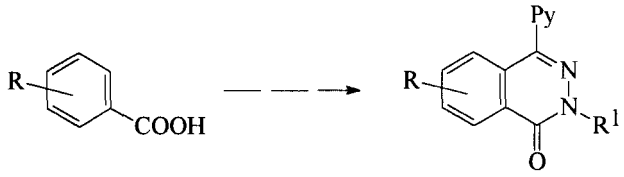
bronchodilatory activities[2,3,4]. It has been found that for this desired biological activity of the phthalazinone systems the essential structural components appeared to be the pyridyl ring at the 4-position of the system **B** and the benzo moiety of the phthalazinone skeleton[2,3,4]. This has promoted a widespread interest in the synthesis of these systems. In particular our attention has been focused on obtaining a synthetic methodology for the corresponding set of the 4-pyridyl-phthalazin-1-ones with diverse substituants at the benzene ring, which are direct starting materials for the preparation of biologically active systems **B** [$R^1$ = Et or 2-(1-imidazolyl)].

The most frequently travelled synthetic route leading to phthalazin-1-ones involves in the first step, the Friedel-Crafts reaction, as a synthetic way of the *ortho*-carbonylated aromatic carboxylic acids, which is usually effected under harsh conditions and does not often proceed with a desired positional selectivity[5,6,7], and in the next step, the conversion of the thus formed *ortho*-carbonylated carboxylic acids upon the reaction with hydrazine[8,9,10,11]. The sequences appeared to be unsatisfactory both in yields and generality. The most attractive route so far reported for the construction of the phthalazin-1-ones is the transformation of readily available 3-hydroxyisoindolin-1-ones upon treatment with hydrazine[12,13]. In a series of recent studies, we have reported[14,15,16] that the secondary carboxyamide moiety provides an excellent possibility for the regiospecific *ortho*-lithiation and subsequent electrophilic substitution of the benzene ring upon treatment of the *ortho*-lithiated species with *N,N*-dimethyl-aromatic amides or the corresponding esters (sources of the benzoyl group) as

a way of transforming the aromatic carboxylic acids into the 3-hydroxy-1*H*-isoindolin-1-ones **3**, **4**, **5**, masked *ortho*-carbonylated amides, which are key starting materials for the phthalazin-1-ones[12,13].

**Scheme 1**

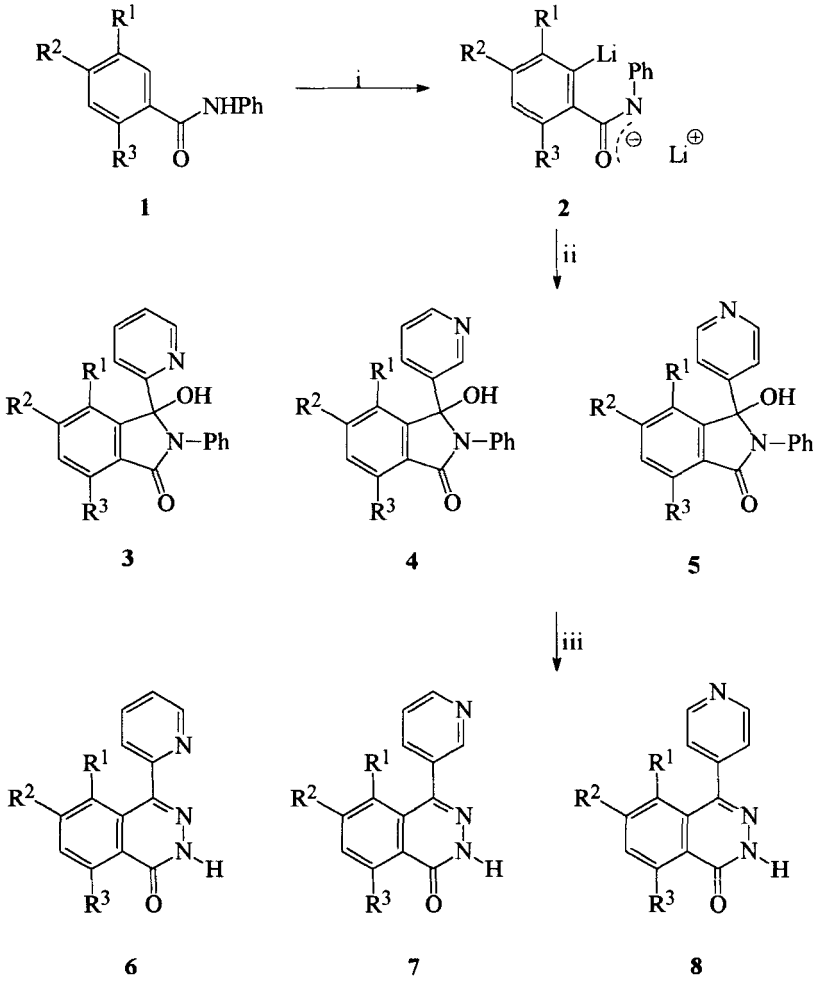



**A** **B**

Our aim was to extend the scope of this general procedure to the synthesis of a series of new regioselectively substituted 4-pyridyl-phthalazin-1-ones and we report the obtained results herein basing upon the reaction of the corresponding 3-hydroxyisoindolin-1-ones with hydrazine. This provides access to an efficient synthetic sequence, as a general strategy, for the transformation of the benzenecarboxylic acids **A** into 4-pyridyl-phthalazinones **B** in a two-step protocol starting from benzoic acids anilides as depicted in the perspective Scheme 1 **(A)→(B)**.

To this end, the anilides **1** were treated in tetrahydrofuran (THF) with 2.1 equivalents of *n*-butyllithium (*n*-BuLi) in the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and converted then into the bis (*N*- and *C*-*ortho*) lithiated anilides **2**. The treatment of the solution of the lithiated species

**Scheme 2**




i. *n*-BuLi in THF/hexane, TMEDA, -78°C→0°C
ii. (a) PyCOOMe, -78°C→0°C; (b) $H_3O^{\oplus}$
iii. $N_2H_4 \cdot H_2O$, Δ

For compounds **1**, **2**, **3**, **4**, **5**, **6**, **7**, **8**
**a**: $R^1 = R^2 = R^3 = H$; **b**: $R^1 = OMe$, $R^2 = H$, $R^3 = H$;
**c**: $R^1 = H$, $R^2 = OMe$, $R^3 = H$; **d**: $R^1 = H$, $R^2 = H$, $R^3 = OMe$

with methyl pyridinecarboxylates afforded the corresponding pyridoylated derivatives, which upon hydrolytic work-up spontaneously cyclized into the 3-hydroxy-3-pyridylisoindolin-1-ones **3**, **4**, and **5**, respectively.

In the final step, in order to achieve progress in the construction of the 4-pyridyl-phthalazin-1-ones **6**, **7**, and **8**, the reaction of the 3-hydroxyisoindolin-1-ones with hydrazine hydrate was undertaken. It was revealed that the isoindolin-1-ones **3**, **4**, and **5** exposed to reacting with boiling neat hydrazine hydrate or in the presence of propan-1-ol, or acetic acid as the solvents furnished the desired phthalazin-1-ones **6**, **7**, and **8** with good yields.

In summary, we have shown a synthetic method for the preparation of 4-pyridyl-phthalazin-1-one **6**, **7**, and **8** with an economy of steps which involves a successive conversion of the benzanilides **1** into the 3-hydroxyisoindolin-1-ones **3**, **4**, and **5** and then their direct conversion into the phthalazin-1-ones **6**, **7**, and **8**.

## EXPERIMENTAL

The melting points were determined using a Boetius hot stage apparatus and they are uncorrected. $^{1}$H-NMR spectra were recorded at 200 MHz and $^{13}$C-NMR spectra at 50 MHz on a Varian Gemini 200 BB spectrometer with $Me_4Si$ used as internal reference. A Zeiss-Jena Specord 71-IR spectrometer was used for the IR spectra. The analytical thin layer chromatography tests (TLC) were carried out on Merck silica gel plates (Kiselgel 60 $F_{254}$, layer thickness 0.2 mm) and the spots were visualised using UV lamp and iodine vapour. The

column chromatography purifications were performed on Merck silica gel (Silica gel 60 0.063-0.100 mm) using 25 g of silica gel per 1 g of the purified material. *n*-Butyllithium in hexane (Aldrich) was each time titrated before use. Tetrahydrofuran (THF) used was purified by it is passage through a column of neutral alumina, heating under reflux over calcium hydride and fractional distillation from it, and it was stored in dark over sodium chip[17]. Commercially available from Aldrich *N,N,N',N'*-tetramethylethylenediamine (TMEDA) (99.5+%) and hydrazine monohydrate (98%) were used without further purification. Benzanilide **1a** was prepared from the commercially available benzoyl chloride, and methoxybenzanilides **1b-d** were prepared from the commercially available methoxybenzoic acids via the corresponding chlorides (obtained from the acids and thionyl chloride) by the Schotten-Baumann method[18].

**General Procedure for the Preparation of Hydroxyisoindolinones 3, 4, 5.**

To the stirred at -78°C under argon solution of anilide **1** (0.020 mol) and TMEDA (4.88 g, 0.042 mol) in THF (60 mL) *n*-BuLi (0.042 mol) was added dropwise. The solution was held at -78°C for 0.25 hour, then allowed to rise to 0°C and kept at this temperature for 0.2 hour. The whole lot was cooled again to -78°C and the solution of methyl pyridinecarboxylate (3.02 g, 0.022 mol) in THF (15 mL) was added dropwise. The reaction mixture after 0.2 hour at -78°C was warmed up to room temperature and kept at this temperature for 2 hours. After that methanol (40 mL) was added and stirring was continued for 0.25 hour. Then

the solvents were removed under reduced pressure. Water (30 mL) was added to the obtained residue and the whole lot was neutralised with the concentrated hydrochloric acid yielding the product which was purified by recrystallization. In the case of compounds **3b** and **3c** the crude materials after neutralisation were purified by column chromatography before recrystallization.



**3-Hydroxy-2-phenyl-3-(2-pyridyl)-2,3-dihydro-1*H*-isoindolin-1-one (3a).**

Yield 60%; mp 195.5-198°C (methanol - water = 1:1); IR (KBr) ν 1715 $cm^{-1}$ (C=O), 2400-3700 $cm^{-1}$ (O-H); $^1$H-NMR (DMSO-$d_6$) δ 8.36 (dd, 1H, 6Py-H, J=1.0 and 4.0 Hz), 7.75-7.89 (m, 4H, Ar-, Py-,OH-H), 7.55-7.60 (m, 2H, Ar-H), 7.35-7.39 (m, 2H, Ar-H), 7.12-7.30 (m, 5H, Ar-, Py-H).

*Anal.* Calcd. for $C_{19}H_{14}N_2O_2$: C, 74.48; H, 4.67; N, 9.27. Found: C, 75.76; H, 4.84; N, 9.30.

**3-Hydroxy-4-methoxy-2-phenyl-3-(2-pyridyl)-2,3-dihydro-1*H*-isoindolin-1-one (3b).**

Yield 55%; (eluent: methylene chloride - ethyl acetate = 9:1, $R_f$=0.16), mp 218-221°C (ethanol), (lit.[15] mp 226-227°C).

**3-Hydroxy-5-methoxy-2-phenyl-3-(2-pyridyl)-2,3-dihydro-1*H*-isoindolin-1-one (3c).**

Yield 60%; (eluent: methylene chloride - ethyl acetate = 9:1, $R_f$=0.24), mp 178-182°C (ethanol), (lit.[15] mp 184-186°C).

**3-Hydroxy-7-methoxy-2-phenyl-3-(2-pyridyl)-2,3-dihydro-1*H*-isoindolin-1-one (3d).**

Yield 62%; mp 170-172°C (ethanol - water = 1:1), (lit.[15] mp 167-168°C).

**3-Hydroxy-2-phenyl-3-(3-pyridyl)-2,3-dihydro-1*H*-isoindolin-1-one (4a).**

Yield 73%; mp 240-242°C (methanol); IR (KBr) ν 1690 $cm^{-1}$ (C=O), 3200-3750 $cm^{-1}$ (O-H); $^1$H-NMR (DMSO-$d_6$) δ 8.61 (d, 1H, 2Py-H, J=1.7 Hz), 8.43 (dd, 1H, 6Py-H, J=1.5 and 4.7 Hz), 7.93 (s, 1H, OH-H), 7.83-7.91 (m, 1H, Ar-H), 7.46-7.77 (m, 5H, Py-, Ar-H), 7.08-7.42 (m, 5H, Py-, Ar-H).

*Anal.* Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.47; H, 4.71, 9.23.

**3-Hydroxy-4-methoxy-2-phenyl-3-(3-pyridyl)-2,3-dihydro-1*H*-isoindolin-1-one (4b).**

Yield 55%; mp 219-220°C (methanol); IR (KBr) ν 1680 $cm^{-1}$ (C=O), 2400-3540 $cm^{-1}$ (O-H); $^1$H-NMR (DMSO-$d_6$) δ 8.54 (d, 1H, 2Py-H, J=1.8 Hz), 8.37 (d, 1H, 6Py-H, J=4.7 Hz), 7.73 (s, 1H, OH-H), 7.54-7.70 (m, 2H, Ar-H), 7.36-7.50 (m, 3H, Py-, Ar-H), 7.10-7.34 (m, 5H, Py-, Ar-H), 3.65 (s, 3H, $CH_3$-H).

*Anal.* Calcd. for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.48; N, 8.43. Found: C, 72.00; H, 5.01; N, 8.51.

**3-Hydroxy-5-methoxy-2-phenyl-3-(3-pyridyl)-2,3-dihydro-1*H*-isoindolin-1-one (4c).**

Yield 75%; mp 245.5-246.5°C (acetic acid - water = 1:1); IR (KBr) ν 1695 $cm^{-1}$ (C=O), 2380-3540 $cm^{-1}$ (O-H); $^1$H-NMR: (DMSO-$d_6$) δ 8.60 (s, 1H, 2Py-H), 8.42 (d, 1H, 6Py-H, J=4.3 Hz), 7.93 (s, 1H, OH-H), 7.80 (d, 1H, Ar-H, J=8.4 Hz), 7.63-7.74 (m, 1H, Ar-H), 7.44-7.58 (m, 2H, Py-, Ar-H), 7.21-7.36 (m, 3H, Py-, Ar-H), 7.10-7.20 (m, 2H, Ar-H), 6.85 (s, 1H, Ar-H), 3.78 (s, 3H, $CH_3$-H).

*Anal.* Calcd. for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 71.73; H, 5.05; N, 8.44.

**3-Hydroxy-7-methoxy-2-phenyl-3-(3-pyridyl)-2,3-dihydro-1*H*-isoindolin-1-one (4d).**

Yield 70%; mp 232-234°C (methanol - water = 2:1); IR (KBr) ν 1695 $cm^{-1}$ (C=O), 2670-3560 $cm^{-1}$ (O-H); $^1$H-NMR: (DMSO-$d_6$) δ 8.59 (d, 1H, 2Py-H, J=2.0 Hz), 8.41 (dd, 1H, 6Py-H, J=1.4 and 4.8 Hz), 7.79 (s, 1H, OH-H), 7.65-7.74 (m, 1H, Py-H), 7.52-7.64 (m, 1H, Ar-H), 7.42-7.52 (m, 2H, Ar-H), 7.21-7.33 (m, 3H, Py-, Ar-H), 7.06-7.19 (m, 2H, Ar-H), 6.86 (d, 1H, 4-H, J=7.4 Hz), 3.93 (s, 3H, $CH_3$-H); $^{13}$C-NMR (DMSO-$d_6$) δ 164.6 (CO-C), 156.7, 151.0, 148.9 147.3, 136.2, 135.7, 135.1, 133.9, 128.3, 125.8, 125.7, 123.2, 116.1, 114.6, 112.3, 89.8, 55.7 ($CH_3$-C).

*Anal.* Calcd. for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 72.31; H, 4.97; N, 8.46.

**3-Hydroxy-2-phenyl-3-(4-pyridyl)-2,3-dihydro-1*H*-isoindolin-1-one (5a).**

Yield 72%; mp 269.5-271.5°C (acetic acid - water = 1:1); IR (KBr) ν 1710 $cm^{-1}$ (C=O), 2400-3700 $cm^{-1}$ (O-H); $^1$H-NMR (DMSO-$d_6$) δ 8.48 (d, 2H, 2Py-, 6Py-H, J=5.9 Hz), 8.00 (s, 1H, OH-H), 7.87-7.94 (m, 1H, Ar-H), 7.52-7.70 (m, 4H, Ar-H), 7.24-7.42 (m, 5H, Py-, Ar-H), 7.10-7.20 (m, 1H, Ar-H); $^{13}$C-NMR (DMSO-$d_6$) δ 166.2 (CO-C), 149.8, 148.8, 148.2, 136.0, 133.3, 129.7, 128.4, 125.9, 125.4, 123.2, 122.7, 120.9, 91.1.

*Anal.* Calcd. for $C_{19}H_{14}N_2O_2$: C, 75.48; H, 4.67; N, 9.27. Found: C, 75.24; H, 4.54; N, 9.32.

**3-Hydroxy-4-methoxy-2-phenyl-3-(4-pyridyl)-2,3-dihydro-1*H*-isoindolin-1-one (5b).**

Yield 75%; mp 296-298.5°C (propan-1-ol), (lit.[15] mp 288-289°C).

**3-Hydroxy-5-methoxy-2-phenyl-3-(4-pyridyl)-2,3-dihydro-1*H*-isoindolin-1-one (5c).**

Yield 64%; mp 281.5-286.5°C (acetic acid - water = 6:4), (lit.[15] mp 283-285°C).

**3-Hydroxy-7-methoxy-2-phenyl-3-(4-pyridyl)-2,3-dihydro-1*H*-isoindolin-1-one (5d).**

Yield 62%; mp 286-289°C (ethanol), (lit.[15] mp 282-284°C).

**Preparation of 4-Pyridyl-2*H*-phthalazin-1-ones 6, 7, 8.**

**Procedure A.** The hydroxyisoindolinone **3**, **4**, **5** (0.020 mol) and the hydrazine monohydrate (3 mL) were heated under reflux for 2 hours. The excess of hydrazine monohydrate was then removed under reduced pressure, water (5 mL) was added to the residue and the whole lot was neutralized with the glacial acetic acid. The separated product was filtered and purified by recrystallization.

**Procedure B.** The hydroxyisoindolinone **3**, **4**, **5** (0.020 mol) and the hydrazine monohydrate (1.5 mL) in propan-1-ol (10 mL) or acetic acid (10 mL) were heated under reflux until the analysis (TLC, ethyl acetate) of the reaction mixture indicated the absence of the starting material **3**, **4**, **5**. After the reaction was completed all the volatile materials were removed under reduced pressure and the residue was worked -up and purified like the one obtained in Procedure A.

**4-(2-Pyridyl)-2*H*-phthalazin-1-one (6a).**

Procedure A, yield 74%; mp 235.5-238°C (ethanol - water = 3:2); IR (KBr) ν 1684 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$) δ 13.00 (s, 1H, NH-H), 8.77 (ddd, 1H, 6Py-H, J=0.9, 1.7 and 4.8 Hz), 8.33-8.42 (m, 2H, Py-, Ar-H), 7.85-8.07 (m, 4H, Py-, Ar-H), 7.56 (ddd, 1H, 5-H, J=1.3, 4.8 and 7.5 Hz); $^{13}$C-NMR (DMSO-$d_6$) δ 159.3 (CO-C), 154.3, 148.5, 143.8, 137.4, 133.2, 131.5, 128.5, 127.9, 127.3, 125.7, 124.0, 123.7.

*Anal.* Calcd. for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.98; H, 4.13; N, 18.65.

**5-Methoxy-4-(2-pyridyl)-2*H*-phthalazin-1-one (6b).**

Procedure B, solvent propan-1-ol, time of reaction 34 hours, yield 62%; mp 252-256°C (propan-1-ol); IR (KBr) ν 1665 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$) δ 12.83 (s, 1H, NH-H), 8.57 (ddd, 1H, 6Py-H, J=1.0, 1.8 and 4.8 Hz), 7.79-7.93 (m, 3H, Py-, Ar-H), 7.39-7.51 (m, 3H, Py-, Ar-H), 3.44 (s, 3H, $CH_3$-H); $^{13}$C-NMR (DMSO-$d_6$) δ 158.8 (CO-C), 157.2, 155.5, 147.9, 144.0, 136.0, 133.0, 129.2, 122.6, 122.5, 118.9, 117.4, 115.6, 56.0 ($CH_3$-C).

*Anal.* Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 65.85; H, 4.30; N, 16.25.

**6-Methoxy-4-(2-pyridyl)-2*H*-phthalazin-1-one (6c).**

Procedure B, solvent propan-1-ol, time of reaction 34 hours, yield 74%; mp 221-225°C (methanol); IR (KBr) ν 1688 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$) δ

12.87 (s, 1H, NH-H), 8.77 (d, 1H, 6Py-H, J=4.4 Hz), 8.27 (d, 1H, 8-H, J=8.9 Hz), 7.86-8.06 (m, 3H, Py-, Ar-H), 7.45-7.58 (m, 2H, Py-, Ar-H), 3.87 (s, 3H, $CH_3$-H); $^{13}$C-NMR (DMSO-$d_6$) δ 162.5 (CO-C), 159.0, 154.4, 148.4, 142.9, 137.4, 130.4, 128.0, 123.8, 123.7, 121.5, 119.7, 109.3, 55.5 ($CH_3$-C).

*Anal.* Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.01; H, 4.38; N, 16.62.

**8-Methoxy-4-(2-pyridyl)-2*H*-phthalazin-1-one (6d).**

Procedure B, solvent propan-1-ol, time of reaction 45 hours, yield 66%; mp 276.5-280°C (ethanol); IR (KBr) ν 1660 cm$^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$) δ 12.60 (s, 1H, NH-H), 8.73 (d, 1H, 6Py-H, J=4.3 Hz), 7.96-8.04 (m, 1H, Ar-H), 7.63-7.84 (m, 3H, Py-, Ar-H), 7.50-7.57 (m, 1H, Ar-H), 7.40 (d, 1H, 5-H, J=8.3 Hz), 3.93 (s, 3H, $CH_3$-H); $^{13}$C-NMR (DMSO-$d_6$) δ 159.4 (CO-C), 157.7, 154.6, 148.5, 143.6, 137.4, 134.3, 130.9, 124.2, 123.6, 118.5, 116.6, 113.4, 56.00 ($CH_3$-H).

*Anal.* Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 65.43;H, 4.40; N, 16.62.

**4-(3-Pyridyl)-2*H*-phthalazin-1-one (7a).**

Procedure A, yield 90%; mp 275.5-277.5°C (methanol); IR (KBr) ν 1680 cm$^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$) δ 13.00 (s, 1H, NH-H), 8.81 (d, 1H, 2Py-H, J=1.3 Hz), 8.75 (dd, 1H, 6Py-H, J=1.0 and 4.5 Hz), 8.33-8.41 (m, 1H, Ar-H),

8.04-8.10 (m, 1H, Py-H), 7.89-7.98 (m, 2H, Ar-H), 7.58-7.71 (m, 2H, Ar-, Py-H).

*Anal.* Calcd. for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.92; H, 4.21; N, 18.69.

**5-Methoxy-4-(3-pyridyl)-2*H*-phthalazin-1-one (7b).**

Procedure B, solvent propan-1-ol, time of reaction 30 hours, yield 80%; mp 275-277°C (propan-1-ol); IR (KBr) ν 1668 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$) δ 12.96 (s, 1H, NH-H), 8.59-8.62 (m, 2H, 2Py-, 6Py-H), 7.79-7.96 (m, 3H, Py-, Ar-H), 7.41-7.49 (m, 2H, Py-, Ar-H), 3.55 (s, 3H, $CH_3$-H); $^{13}$C-NMR (DMSO-$d_6$) δ 158.7 (CO-C), 155.4, 148.6, 148.3, 141.8, 135.8, 135.3, 133.0, 129.3, 122.1, 118.6, 117.7, 115.7, 55.7 ($H_3C$-C).

*Anal.* Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.16; H, 4.44; N, 16.57.

**6-Methoxy-4-(3-pyridyl)-2*H*-phthalazin-1-one (7c).**

Procedure A, yield 78%; mp 241-243°C (acetic acid - water = 1:1); IR (KBr) ν 1670 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$) δ 13.2 (s, 1H, NH-H), 8.8-9.4 (m, 2H, 2Py-, 6Py-H), 8.2-8.7 (m, 2H, Py-, Ar-H), 7.6-8.1 (m, 2H, Py-, Ar-H), 7.3 (d, 1H, 5-H, J=2.5 Hz), 4.1 (s, 3H, $CH_3$-H).

*Anal.* Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.27; H, 4.32; N, 16.52.

**8-Methoxy-4-(3-pyridyl)-2*H*-phthalazin-1-one (7d).**

Procedure B, solvent propan-1-ol, time of reaction 35 hours, yield 78%; mp 255-259°C (propan-1-ol); IR (KBr) ν 1670 $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$) δ 12.60 (s, 1H, NH-H), 8.70-8.73 (m, 2H, 2Py-, 6Py-H), 7.96-8.02 (m, 1H, Py-H), 7.76-7-85 (m, 1H, Ar-H), 7.57 (ddd, 1H, Py-H, J=0.8, 4.9 and 7.9 Hz), 7.42 (d, 1H, Ar-H, J=8.0 Hz), 7.07 (dd, 1H, Ar-H, J=0.7 and 8.0 Hz), 3.93 (s, 3H, $CH_3$-H). $^{13}$C-NMR (DMSO-$d_6$) δ 159.7 (CO-C), 157.6, 149.7, 149.5, 143.1, 136.9, 134.7, 131.5, 131.3, 123.4, 117.6, 116.5, 113.8, 56.1 ($CH_3$-C).

*Anal.* Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.39; H, 4.35; N, 16.35.

**4-(4-Pyridyl)-2*H*-phthalazin-1-one (8a).**

Procedure A, yield 75%; mp 301-302°C (ethanol); IR (KBr) ν 1675 $cm^{-1}$ (C=O); $^1$H-NMR δ 13.04 (s, 1H, NH-H), 8.78 (dd, 2H, 2Py-, 6Py-H, J=1.6 and 4.4 Hz), 8.34-8.39 (m, 1H, Ar-H), 7.91-7.98 (m, 2H, Ar-H), 7.63-7.72 (m, 3H, Py-, Ar-H).

*Anal.* Calcd. for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 70.02; H, 4.17; N, 18.82.

**5-Methoxy-4-(4-pyridyl)-2*H*-phthalazin-1-one (8b).**

Procedure B, solvent acetic acid, time of reaction 65 hours, yield 79%; mp 290-293°C (ethanol); IR (KBr) ν $cm^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$) δ 12.97

(s, 1H, NH-H), 8.62 (d, 2H, 2Py-, 6Py-H, J=5.9 Hz), 7.81-7.94 (m, 2H, Ar-H), 7.38-7.50 (m, 3H, 3Py-, 5Py-, Ar-H), 3.54 (s, 3H, $CH_3$-H); $^{13}$C-NMR (DMSO-$d_6$) δ 158.7 (CO-C), 155.3, 148.5, 147.1, 142.3, 133.1, 129.2, 123.3, 118.1, 117 7, 115.8, 55.5 ($CH_3$-C).

*Anal.* Calcd. for $C_{14}H_{11}N_3O_2$: N, 16.59. Found: N, 16.87.



**6-Methoxy-4-(4-pyridyl)-2*H*-phthalazin-1-one (8c).**

Procedure B, solvent propan-1-ol, time of reaction 60 hours, yield 78%; mp 244-249°C (propan-1-ol); IR (KBr) ν 1666 cm$^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$) δ 12.92 (s, 1H, NH-H), 8.77 (d, 2H, 2Py-, 6Py-H, J=5.8 Hz), 8.28 (d, 1H, 8-H, J=8.9 Hz), 7.67 (d, 2H, 3Py-, 5Py-H, J=5.9 Hz), 7.50 (dd, 1H, 7-H, J=2.5 and 8.8 Hz), 7.03 (d, 1H, 5-H, J=2.4 Hz), 3.86 (s, 3H, $CH_3$-H); $^{13}$C-NMR (DMSO-$d_6$) δ 162.8 (CO-C), 158.8, 149.9, 143.5, 142.5, 130.0, 128.4, 123.7, 121.2, 120.2, 107.5, 55.6 ($CH_3$-C).

*Anal.* Calcd. for $C_{14}H_{11}N_3O_2$: C, 66.40; H, 4.38; N, 16.59. Found: C, 66.08; H, 4.45; N, 16.37.

**8-Methoxy-4-(4-pyridyl)-2*H*-phthalazin-1-one (8d).**

Procedure B, solvent acetic acid, time of reaction 35 hours, yield 55%, mp 283-289°C (methanol); IR (KBr) ν 1690 cm$^{-1}$ (C=O); $^1$H-NMR (DMSO-$d_6$) δ 12.63 (s, 1H, NH-H), 8.75 (d, 2H, 2Py-, 6Py-H, J=5.9 Hz), 7.76-7.85 (m, 1H, Ar-H), 7.57 (dd, 2H, 3Py-, 5Py-H, J=1.5 and 4.4 Hz), 7.42 (d, 1H, Ar-H,

J=8.3 Hz), 7.12 (d, 1H, 5-H, J=8.0 Hz), 3.93 (s, 3H, $CH_3$-H).

*Anal*. Calcd. for $C_{14}H_{11}N_3O_2$: N, 16.59. Found: N, 16.26.

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