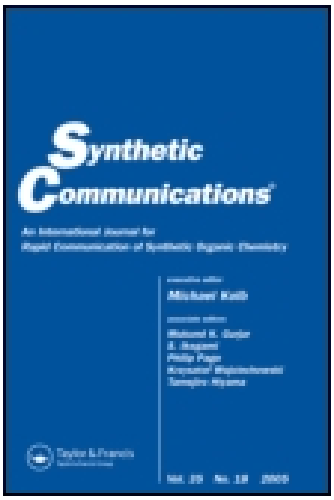

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Synthesis of Some Novel N-Substituted Phthalazinone and Pyridopyridazinone Derivatives

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SYNTHESIS OF SOME NOVEL *N*-SUBSTITUTED PHTHALAZINONE AND PYRIDOPYRIDAZINONE DERIVATIVES

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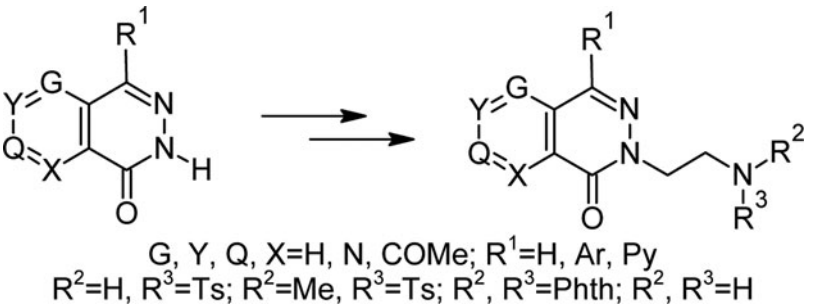
GRAPHICAL ABSTRACT



Abstract *Phthalazinone and pyridopyridazinone derivatives* ***3, 5****, and* ***9*** *were prepared via reaction of appropriate lactams* ***2*** *and* ***8*** *with 2-bromoethylphthalimide,* N*-tosylaziridine, and* N,O*-ditosyl derivatives of* N*-methylethanolamine in a two-step process in the presence of MeONa/MeOH or NaH/dimethylformamide (DMF). Starting compounds* ***2*** *and* ***8*** *were obtained by reaction of hydrazine hydrate with isoindolinones* ***1*** *or azaisoindolinones* ***6****. Selected* N*-(2-phthalimidoethyl)-phthalazinones were converted into corresponding 2-[2-(methylamino) ethyl]- derivatives in satisfactory yields by treatment with hydrazine.*

Keywords Alkylation; amines; phthalazinone; pyridopyridazinone

INTRODUCTION

Phthalazinones and azaphthalazinones are an interesting group of organic compounds containing a 2*H*-pyridazin-3-one core. Their various derivatives exhibit

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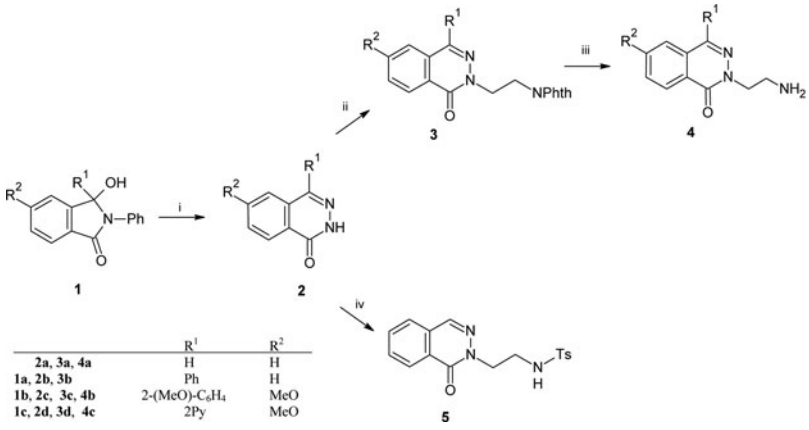
diverse biological activities (e.g., antihypertensive,[1] antimicrobial,[2] antiallergic,[3] and antiplatelet[4]). Moreover, some of these compounds have found use as pigments[5] and plant growth regulators.[6] In the past few years, 2*H*-phthalazin-1-one and its derivatives were also tested as corrosion inhibitors. It has been shown that in acidic media these type of compounds efficiently inhibit corrosion of aluminium, mild steel, and copper.[7]

Continuing our research interest in the synthesis and modification of nitrogen heterocycles,[8,9] in the present communication, we report results of the preparation of some phthalazinone and especially pyridopyridazinone derivatives containing at the lactam nitrogen atom (2-phthalimidoethyl)-, [2-(tosylamino)ethyl]-, and [2-(methyl(tosyl)amino)ethyl]- substituents, respectively. Furthermore, our interests involve the possible applications of 2*H*-pyridazin-3-one derivatives in the different fields, such as, for example, corrosion protection.

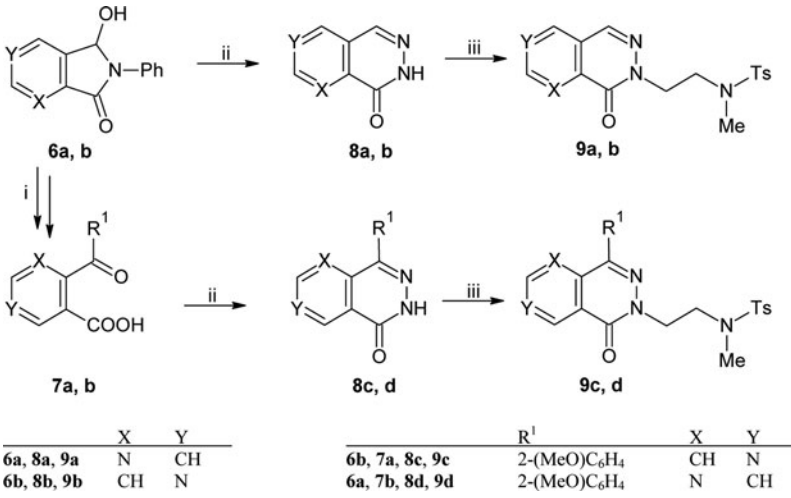
RESULTS AND DISCUSSION

N-(2-Phthalimidoethyl)-, *N*-(2-aminoethyl)-, and *N*-[2-(tosylamino)ethyl]-derivatives of phthalazinones (compounds **3, 4**, and **5**) and *N*-[2-(methyl(tosyl) amino)ethyl]- derivatives of pyridopyridazinones (compounds **9**) were synthesized as shown in Schemes 1 and 2.

The 2*H*-phthalazin-1-ones **2** (Scheme 1) and pyridopyridazinones **8** (Scheme 2) were prepared by reaction of appropriate isoindolinones **1**, their aza analogs **6,** or keto acids **7** with hydrazine, according to described procedures.[8,9] For our studies, we chose 2*H*-phthalazin-1-ones **2** and pyridopyridazinones **8** containing a hydrogen atom, as well as phenyl, 2-methoxyphenyl, and 2-pyridyl substituents at the pyridazinone ring. Azaphthalazinones **8c** and **8d** were synthesized from 2- and 4-(2-methoxybenzoyl) nicotinic acids **7a** and **b**, respectively (Scheme 2) and used without purification for the alkylation step. *ortho*-Benzoylated nicotinic acid derivatives **7a** and **b** were obtained from picolin- and isonicotinanilides.[10]



Scheme 1. Synthesis of compounds **3**–**5**. Reagents and conditions: (i) $NH_2NH_2{\cdot}H_2O$, PrOH, 97 °C; (ii) (*a*) NaH, DMF, rt; (*b*) $BrCH_2CH_2NPhth$, DMF, rt; (iii) $NH_2NH_2{\cdot}H_2O$, EtOH, 78 °C; (iv) (*a*) MeO-Na/MeOH, 65 °C; (*b*) *N*-tosylaziridine, 65 °C.



	X	Y
6a, 8a, 9a	N	CH
6b, 8b, 9b	CH	N

	R^1	X	Y
6b, 7a, 8c, 9c	2-(MeO)C_6H_4	CH	N
6a, 7b, 8d, 9d	2-(MeO)C_6H_4	N	CH

Scheme 2. Synthesis of compounds **8** and **9**. Reagents and conditions: (i) (*a*) KBH_4, MeOH, 20 °C; (*b*) HCl; (*c*) 2-(MeO)C_6H_4Li, THF; (*d*) $KMnO_4$, H_2O-aceton = 1:1; (ii) $NH_2NH_2 \cdot H_2O$, PrOH, 97 °C; (iii) (*a*) MeONa/MeOH, 65 °C; (*b*) $TsOCH_2CH_2N(Me)Ts$, 65 °C.

Afterward, lactams **2** and **8** were converted into derivatives **3, 5**, and **9** in a two-step alkylation process (Schemes 1 and 2) involving in the first stage transformation of compounds **2** or **8** into corresponding sodium salts, and then the final products were prepared via reactions with the various alkylation agents, shown in Fig. 1.[11–13] Compounds **3, 5**, and **9** could effortlessly be converted into corresponding aminoalkyl derivatives, which are useful intermediates in the synthesis of a variety of significant compounds.[14]

Phthalimidoethylphthalazinones **3** were prepared by reacting of starting phthalazinones **2** with 2-(2-bromoethyl)-1*H*-isoindole-1,3-(2*H*)-dione, in the presence of NaH in dry dimethylsulfoxide (DMF) as solvent, at ambient temperature (Scheme 1). Products **3** were isolated by precipitation with water in moderate yields. Treatment of derivatives **3** with hydrazine in refluxing EtOH led to the analogs **4** containing free amine group (Scheme 1). 2-Aminoethylphthalazinone **4a** was isolated by column chromatography in 50% yield.[14]

In the case of synthesis of compound **5** (Scheme 1), 2*H*-phthalazin-1-one was alkylated with *N*-tosylaziridine in the presence of MeONa in dry MeOH, giving *N*-tosylaminoethyl derivative. The reaction was completed in 10 h and after the neutralization by solution of HCl (1:1), product was separated in 55% yield. Benzenesulfonamides **9** (Scheme 2) were obtained under similar conditions. Treatment of pyridopyridazinones **8** with ditosylated 2-(methylamino)ethanol in MeOH/MeONa led to the transformation of the starting material and gave *N*-[(*N*-Metyl-*N*-tosylamino)ethyl]- derivatives **9** in ca. 60% yields.

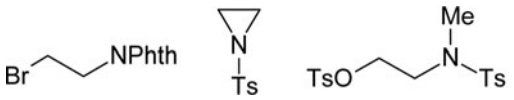


Figure 1. Alkylation agents.

The identity of isolated phthalazinone and pyridopyridazinone derivatives **3, 4, 5**, and **9** (Schemes 1 and 2) was confirmed by microanalysis and NMR, infrared (IR), and mass (MS) spectroscopy. In all experiments, we only observed the formation of *N*-alkylated products **3, 5**, and **9**. Melting points, yields, and spectral data are shown in the experimental section and presented in the supporting information. Additionally, we have performed the preliminary studies of inhibitory properties of selected synthetized compounds on the corrosion of bearing steel 100Cr6 in acidic media using the potentiodynamic polarization method. The initial results suggest that compounds **3d** and **9b** can act as corrosion inhibitors.

CONCLUSIONS

In summary, we described an efficient route to synthesize of *N*-substituted derivatives of phthalazinones and pyridopyridazinones via an alkylation reaction with 2-bromoethylphthalimide, *N*-tosylaziridine, and *N,O*-ditosyl-*N*-methylethanolamine. Because of the ease of future transformation of the obtained derivatives, they could be valuable materials in organic synthesis.

EXPERIMENTAL

The melting points were determined on a Boetius hot-stage apparatus and 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 tetramethylsilane (TMS) as an internal reference. IR spectra were recorded on a Nexus FT-IR spectrometer. Mass spectra analyses were performed on mass spectrometer MAT95, Finnigan. 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 visualized using an ultraviolet lamp.

3-Hydroxy-1*H*-isoindolin-1-ones **1**, pyrrolopyridinones **7**, 2*H*-phthalazin-1-ones **2**, pyridopyridazinones **8**, *N*-(2-bromoethyl)phthalimide, *N*-tosylaziridine, and toluene-4-sulfonic acid 2-[methyl-(toluene-4-sulfonyl)-amino]-ethyl ester were prepared according to an already reported procedure.[8–13] Reagents were purchased from Sigma-Aldrich/Fluka and used without further purification. Solvents were purified by conventional methods.

The ^{1}H NMR spectra of compounds **3, 4, 5**, and **9** showed two characteristic signals attributable to two groups of methylene protons and additionally, for derivatives **5** and **9,** the presence of singlets at 2.30–2.36 ppm and 2.90–2.92 ppm corresponding to a methyl group of 4-toluenesulfonyl moiety and N-Me protons, respectively. The ^{1}H NMR spectra of **4** displayed the presence of the primary amine protons as characteristic broad singlets at 1.40–1.75 ppm.

General Procedure for Preparation of 2-[2-(1-Oxo-1*H*-phthalazin-2-yl)-ethyl]-isoindole-1,3-diones 3

The reaction was carried out under argon. A solution of 2*H*-phthalazin-1-one **2** (3.95×10^{-3} mol) in dry DMF (50 cm^3) was added slowly to a stirred suspension of sodium hydride (4.25 mol) in dry DMF (10 cm^3). The reaction mixture was stirred

at room temperature for 45 min. Next, the whole lot was cooled to 0 °C and the solution of *N*-(2-bromoethyl)phthalimide (5.92×10^{-3} mol) in dry DMF (10 cm^3) was added in portions. At first the mixture was kept for 5 h at 0 °C and later for 16 h at ambient temperature. After this time the reaction mixture was poured into an ice-water mixture (100 cm^3) and next extracted with $CHCl_3$ (3×50 cm^3). The combined extracts were dried over $MgSO_4$ and concentrated under vacuum. The isoindole-1,3-dione **3** was isolated by column chromatography or crystallization.

2-{2-[6-Methoxy-4-(2-methoxyphenyl)-1-oxo-1*H*-phthalazin-2-yl]-ethyl}-isoindole-1,3-dione (3c)

Yield: 50%; mp 180–184 °C; $R_f = 0.72$ (AcOEt–toluene 1:1); IR (KBr, cm^{-1}): $\nu = 1710$, 1653 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6, ppm): $\delta = 8.21$ (d, 1H, 8-ArH, $J = 8.9$ Hz), 7.88–7.79 (m, 4H, ArH), 7.47–7.37 (m, 2H, ArH), 7.10 (d, 1H, ArH, $J = 8.4$ Hz), 6.77 (m, 1H, ArH), 6.58 (dd, 1H, ArH, $J = 7.4$, 1.7 Hz), 6.47 (d, 1H, 5-ArH, $J = 2.4$ Hz), 4.72–4.63 (m, 1H, CH_2), 4.14–4.03 (m, 3H, CH_2), 3.73 (s, 3H, OMe), 3.63 (s, 3H, OMe); ^{13}C NMR (50 MHz, DMSO-d_6, ppm): $\delta = 167.6$, 162.5, 158.1, 156.8, 144.3, 134.4, 131.4, 131.1, 130.8, 130.2, 128.3, 123.1, 120.3, 120.0, 111.3, 108.1, 55.5, 55.2, 48.4, 36.1. Anal. calcd. for ($C_{26}H_{21}N_3O_5$): C, 68.56; H, 4.65; N, 9.23%. Found: C, 68.54; H, 4.76; N, 9.21%.

Synthesis of Amines 4

Hydrazine monohydrate (98%, 4.04×10^{-3} mol, 0.2 cm^3) was added to a solution of phthalimido- derivative of phthalazinone **3** (1.49×10^{-3} mol) in dry EtOH (15 cm^3). The mixture was heated to boiling until TLC analysis ($CHCl_3$/MeOH 19/1) indicated the absence of a starting lactam. After the reaction was completed, the mixture was cooled to ambient temperature and acidified by addition of a hydrochloric acid and next all was again heated to boiling for 30 min. After this time, the mixture was again cooled to ambient temperature and the separated product was filtrated off. The filtrate was alkalized by a solution of 40% KOH. In next step the solution was extracted with CH_2Cl_2 (3×50 cm^3). The combined extracts were dried over $MgSO_4$ and concentrated under vacuum. The amine was isolated by column chromatography.

Amines **4b** and **4c** were unstable and their full analysis was difficult. For these compounds only IR, NMR, and MS spectra were recorded.

2-(2-Aminoethyl)-2*H*-phthalazin-1-one (4a)[14]

Yield: 50% (oil) (mp 84–88 °C[14]); $R_f = 0.04$ (AcOEt–MeOH 3:1, next MeOH); IR (KBr, cm^{-1}): $\nu = 3330$, 3290 (NH), 1656 (C=O); ^{1}H NMR (200 MHz, $CDCl_3$, ppm): $\delta = 8.50$–8.40 (m, 1H, ArH), 8.20 (s, 1H, 4-pyridH), 7.90–7.70 (m, 3H, ArH), 4.33 (t, 2H, CH_2, $J = 6.2$ Hz), 3.19 (t, 1H, CH_2, $J = 6.2$ Hz), 1.40 (s, 2H, NH_2) ppm; ^{13}C NMR (50 MHz, $CDCl_3$, ppm): $\delta = 157.0$, 138.1, 133.3, 131.9, 129.8, 128.0, 126.9, 126.2, 53.8, 41.0.

Preparation of 4-Methyl-*N*-[2-(1-oxo-1*H*-phthalazin-2-yl)-ethyl]-benzenesulfonamide (5)

To a solution of sodium methoxide (1.52×10^{-2} mol) in dry MeOH (40 cm^3) was added 2*H*-phthalazin-1-one **2** (0.0137 mol). The mixture was heated under reflux for 30 min. Afterward, *N*-tosylaziridine (1.64×10^{-2} mol) was added and heating was continued for another 10 h. Then the mixture was cooled to ambient temperature and neutralized by solution of hydrochloric acid (1:1). The separated product was filtrated, washed with dry MeOH, and purified by recrystallization from AcOEt.

Yield 55%; mp 209–212 °C (AcOEt); IR (KBr, cm^{-1}): $\nu = 3162$ (NH), 1636 (C=O); ^{1}H NMR (200 MHz, DMSO-d_6, ppm): $\delta = 8.39$ (s, 1H, 4-pyridH), 8.23 (d, 1H, 5-ArH, J = 7.2 Hz), 7.82–7.74 (m, 3H, 6,7,8-ArH), 7.77 (t, 1H, NH, J = 6.3 Hz), 7.61 (d, 2H, TsH, J = 8.0 Hz), 7.28 (d, 2H, TsH, J = 8.0 Hz), 4.17 (t, 2H, CH_2, J = 6.3 Hz), 3.18 (m, 2H, CH_2) 2.30 (s, 3H, Me); ^{13}C NMR (50 MHz, DMSO-d_6, ppm): $\delta = 158.3$, 142.2, 137.7, 137.3, 133.1, 131.6, 129.2, 129.1, 126.8, 126.5, 126.1, 125.4, 49.8, 20.8. Anal. calcd. for ($C_{17}H_{17}N_3O_3S$): C, 59.46; H, 4.99; N, 12.24; S, 9.34%. Found: C, 59.52; H, 4.97; N, 12.31; S, 9.19%.

General Procedure for Preparation of Benzenesulfonamides 9

Pyridopirydazinone **8** (1.53×10^{-2} mol) was added to a solution of sodium methoxide (1.65×10^{-2} mol) in dry MeOH (70 cm^3). The mixture was heated to boiling for 30 min. Afterward, toluene-4-sulfonic acid 2-[methyl-(toluene-4-sulfonyl)-amino]-ethyl ester (0.0230 mol) was added and heating was continued for the next 7 h. After this time, the mixture was cooled to ambient temperature. The separated product was filtrated off, washed with dry MeOH, and purified by crystallization or column chromatography.

4,*N*-Dimethyl-*N*-[2-(1-oxo-1*H*-pyrido[3,4-*d*]pyridazin-2-yl)-ethyl]-benzenesulfonamide (9b)

Yield: 50%; mp 157–159 °C (MeOH); IR (KBr, cm^{-1}): $\nu = 1655$ (C=O); ^{1}H NMR (200 MHz, $CDCl_3$, ppm): $\delta = 9.15$ (s, 1H, ArH), 8.98 (d, 1H, ArH, J = 4.9 Hz), 8.28 (s, 1H, ArH), 8.18 (d, 1H, ArH, J = 5.5 Hz), 7.60 (d, 2H, TsH, J = 8.0 Hz), 7.20 (d, 2H, TsH, J = 8.0 Hz), 4.42 (t, 2H, CH_2, J = 5.8 Hz), 3.51 (t, 2H, CH_2, J = 5.8 Hz), 2.91 (s, 3H, NMe), 2.36 (s, 3H, TsMe); ^{13}C NMR (50 MHz, $CDCl_3$, ppm): $\delta = 157.9$, 150.6, 149.1, 143.1, 135.7, 134.8, 132.5, 129.4, 127.0, 123.9, 118.9, 48.7, 48.0, 35.1, 21.5. Anal. calcd. for ($C_{17}H_{18}N_4O_3S$): C, 56.97; H, 5.06; N, 15.63; S, 8.95%. Found: C, 57.01; H, 5.09; N, 15.68; S, 8.95%.

FUNDING

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SUPPORTING INFORMATION

Full experimental details, ^{1}H and ^{13}C NMR data, and IR spectra for this article can be accessed on the publisher's website.

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