SYNTHESIS OF N-(2-(METHYLAMINO)ETHYL) DERIVATIVES OF 2H-PHTHALAZIN-1-ONES

Zbigniew Malinowski,1 Aleksandra K. Szczęśniak,1 Wanda Pakulska,2 Dariusz Sroczyński,3 Elżbieta Czarnecka,2 and Jan Epsztajn1

1Faculty of Chemistry, Department of Organic Chemistry, University of Łódź, Łódź, Poland
2Faculty of Pharmacy, Department of Pharmacodynamics, Medical University of Łódź, Łódź, Poland
3Faculty of Chemistry, Department of Inorganic and Analytical Chemistry, University of Łódź, Łódź, Poland

GRAPHICAL ABSTRACT

Abstract A series of new alkyl, tosyl, acetyl, and tert-butoxycarbonyl derivatives of 2-(2-aminoethyl)-phthalazinones were efficiently synthesized by reaction of lactams with N-Boc-, N-acetyl-, or N,O-ditosyl derivatives of N-methylethanolamine in the presence of MeONa or under Mitsunobu reaction conditions. Selected compounds were converted into corresponding 2-[2-(methylamino)ethyl]phthalazinones in good yields.

Keywords Alkylation; amines; Mitsunobu reaction; phthalazinones; rotamers

INTRODUCTION

2H-Pyridazin-3-ones and their benzo- (phthalazinones) and pyrido- (pyridopyridazinones) derivatives demonstrate a wide spectrum of biological properties. Compounds of these type show an interesting pharmacological action (e.g., adenosine A1 receptor antagonist I,[1] antinociceptive agents II,[2–4] α1-adrenoreceptors antagonist III,[5,6] and nonprostanoid PGI2 agonist IV,[7]; Fig. 1).

Especially interesting group of 2H-pyridazin-3-one derivatives are compounds substituted at the lactam nitrogen atom by ω-aminoalkyl group. These type of
compounds can exhibit analgesic as well as nonsteroidal anti-inflammatory activity Va–c.\textsuperscript{[8–11]}

In our previous articles we have described methodologies for the synthesis of novel (dimethylamino)methyl- and 2-(dimethylamino)ethyl- derivatives of phthalazinones and pyridopyridazinones (Scheme 1).\textsuperscript{[11,12]} The synthetic methods applied in the preparation of these compounds were based on the Mannich reaction and on the reaction of lactams I with 2-chloro-\(N,N\)-dimethylethanamine.

**RESULTS AND DISCUSSION**

In this article, we present methods for the preparation of 2-(\(N\)-methylamino)ethyl- derivatives of phthalazinones. Starting lactams I were synthesized from the appropriate 3-hydroxyisoindolinones or ketoacids upon reaction with hydrazine monohydrate, according to previously described methods.\textsuperscript{[11–14]}

Our preliminary studies have shown that preparation of 2-(\(\omega\)-aminoalkyl) phthalazinones by reaction of corresponding 2-halogenethylamines 4 (Scheme 2) with lactams I is not effective. If primary or secondary \(\omega\)-halogenalkylamines 4a,b were used to react with phthalazinones I, the outcomes were rather poor.\textsuperscript{[15]}

![Figure 1. Structures of biologically active 2\(H\)-pyridazin-3-one derivatives I–V.](image-url)
N-Alkylated products 5 were formed in trace amounts only, if at all. The formation of compounds 5 was observed by NMR spectroscopy and they were not isolated in individual form. Therefore, practical application of the ω-halogenalkylamines as alkylating agents is limited and determined by the degree of substitution of amine nitrogen atom. In practice, this methodology plays a significant role in preparation of 2-(N,N-dialkylamino)ethyl-lactam derivatives type 3,[11] solely (Scheme 1).

Based on these results, we focused on the synthesis of selected N-(2-aminooethyl)-phthalazinone derivatives substituted on the amine nitrogen atom by alkyl, tosyl, acetyl, and tert-butoxycarbonyl group. These derivatives can be effortlessly converted into the desired secondary amines (N-methylamines).[16,17] Easily accessible derivatives of 2-(methylamino)ethanol, types 6, 7, and 8 (Fig. 2),[18–20] were used as ω-aminooethylating agents.

Synthesis of N-2-(methylamino)ethyl lactams type 10 was carried out using two approaches as shown in Scheme 3. Initially, benzenesulfonamides 9 were synthesized, as precursors of corresponding 2-(methylamino)ethyl derivatives 10.

Phthalazinones 1 after treatment with MeONa were converted into amides 9 by reaction with ditosylated 2-(methylamino)ethanol, in 40–64% yields. In the second

| Entry | Compound | R¹ | R² |
|-------|----------|----|----|
| 1     | 3a       | H  | H  |
| 2     | 3b       | Me | H  |
| 3     | 3c       | 2-(MeO)-C₆H₄ | MeO |
| 4     | 2a       | 4-Cl-C₆H₄ | MeO |
| 5     | 2b, 3d   | 2Py | MeO |
| 6     | 2c, 3e   | 3Py | MeO |
| 7     | 2d, 3f   | 4Py | MeO |

Scheme 1. Synthesis of (N,N-dimethylamino)alkyl phthalazinones 2 and 3,[11,12]
stage benzenesulfonamides 9 were hydrolyzed to corresponding amines 10 by heating with concentrated H$_2$SO$_4$ (110°C). Desired amines were obtained in 56–78% yields. The structures of compounds 9 and 10 were determined by infrared (IR), $^1$H NMR, and elemental analysis or mass spectroscopy (Table 1).

Unexpectedly, synthesis of amine 10d via hydrolysis of appropriate N-tosyl derivative with H$_2$SO$_4$ ended in failure. For this reason, the synthesis of amine 10d was carried out using the Mitsunobu reaction\cite{21,22} as a key step, followed by deprotection of the amine group. Alkylation of phthalazinone 1 with N-Boc-protected 2-(methylamino)ethanol using standard Mitsunobu conditions (TPP, DEAD) gave carbamic acid derivatives 11e in satisfactory yields (Scheme 3). Cleavage of the Boc protecting group of compound 11e with hydrochloric acid at rt gave the secondary amine 10d in 55% yield. This protocol was successfully applied to
preparation of $N$-(tert-butoxycarbonyl) derivatives 11b,d and $N$-acetyl analogs 11a,c using $N$-(2-hydroxyethyl)-$N$-methylacetamide as a starting material, too. Therefore, presented methods for synthesis of $N$-methylaminoethyl derivatives of phthalazines are complementary to one another but application of Mitsunobu methodology allows the reaction to be carried out under milder conditions.

**CONCLUSIONS**

In conclusion, we described an efficient synthesis of new $N$-substituted phthalazines derivatives containing (2-{methyl[(4-methylphenyl)sulfonyl]amino}ethyl)- and
{2-[(tert-butoxy carbonyl)(methyl)amino]ethyl}- moiety by reaction of series phthalazinones with readily accessible 2-(methylamino)ethanol derivatives. This, coupled with an effective conversion of compounds 9 and 11 to the corresponding 2-[2-(methylamino)ethyl]-2H-phthalazin-1-ones 10, should allow to access a wide variety of these types of compounds.

EXPERIMENTAL

The melting points were determined on a Boetius hot-stage apparatus and are uncorrected. 1H NMR spectra were recorded at 200 MHz and 13C 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 a MAT95-Finnigan mass spectrometer. The analytical thin-layer chromatography tests (TLC) were carried out on Merck silica gel plates (Kieselgel 60 F_{254}, layer thickness 0.2 mm) and the spots were visualized using an ultraviolet lamp.

Commercially available (Aldrich, Fluka) hydrazine monohydrate, N,N,N',N'-tetramethylethylenediamine, triphenylphosphite (TPP), diethyl azodicarboxylate (DEAD), 2-acetylbenzoic acid, and 2-benzoilbenzoic acid were used without further purification. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately before use. ω-Aminoethylating agents 6, 7, and 8 were prepared by standard methods[18–20] from the commercially available 2-(methylamino)ethanol.

2H-Phthalazin-1-ones 1 were prepared according to an already reported procedure from appropriate 3-hydroxy-1H-isoadolin-1-ones or ketoacids.[11–14]

General Procedure for Preparation of Benzenesulfonamides 9

2H-Phthalazin-1-one 1 (0.0153 mol) was added to a solution of sodium methoxide (0.0165 mol) in dry MeOH (70 ml). The mixture was heated to boiling for 30 min. Afterward, toluene-4-sulfonic acid 2-[methyl-(toluene-4-sulfonyl)-amino]-ethyl ester (6) (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 methanol, and purified by crystallization or column chromatography.

The FTIR spectra of the benzenesulfonamides 9 displayed characteristic absorption of the C=O in the region 1640–1650 cm\(^{-1}\). Besides, bands of SO\(_2\) between 1150 and 1340 cm\(^{-1}\) were observed. The 1H NMR spectra of amides 9 showed the presence of two singlets at 2.31–2.34 ppm and 2.91–2.93 ppm corresponding to methyl group of 4-toluenesulfonyl moiety and N-Me protons, respectively. The signals of the ethylene bridge were displayed as two triplets at 4.36–4.50 and 3.51–3.59 ppm.

4,N-Dimethyl-N-[2-(1-oxo-4-phenyl-1H-phthalazin-2-yl)-ethyl] benzenesulfonamide (9c)

Yield 64%; mp 128–131 °C (MeOH); FT-IR (KBr, cm\(^{-1}\) )v: 1654 (C=O), 1336, 1163 (SO\(_2\)); 1H NMR (200 MHz, CDCl\(_3\), ppm) δ: 8.46–8.51 (m, 1H, 8-ArH),
7.82–7.72 (m, 3H, Ph, ArH), 7.67–7.52 (m, 7H; Ph, Ar, TsH), 7.15 (m, 2H, TsH), 4.48 (t, 2H, CH2, J = 6.0 Hz), 3.59 (t, 2H, CH2, J = 6.0 Hz), 2.93 (s, 3H, NMe), 2.31 (s, 3H, TsMe); 13C NMR (50 MHz, CDCl3, ppm) δ: 159.1, 142.9, 135.0, 134.9, 132.7, 131.2, 129.4, 129.0, 128.5, 127.9, 127.0, 126.6, 48.1, 34.8, 21.4. Anal. calcd. for (C24H23N3O3S): C, 66.49; H, 5.35; N, 9.69; S, 7.40%. Found: C, 66.45; H, 5.42; N, 9.73; S, 7.47%.

General Procedure for Preparation of Acetyl- and tert-Butoxycarbonyl-Derivatives of 2-[(Methylamino)ethyl]-2H-phthalazin-1-ones 11 (Mitsunobu Procedure)

The Mitsunobu reaction was carried out under argon. DEAD (0.0102 mol, solution in toluene c ≈ 40%) was slowly added to a stirred solution of TPP (0.0102 mol) in dry THF (10 ml) at −10°C. Then a solution of phthalazinone 1 (0.0068 mol) in THF (44 ml) was added dropwise. The whole lot was mixed for 15 min at −10°C and next the appropriate derivative of N-methylethanolamine 7 or 8 (0.00748 mol) in THF (5 ml) was added at −10°C. The mixture was stirred during 2 h at −10°C, after which time the reaction mixture was warmed to ambient temperature and stirred in this condition for 20 h. All volatile materials were removed under reduced pressure, ethyl ether (20 ml) was added to the residue, and the whole lot was stirred for 0.5 h at ambient temperature. The separate white solid was collected by filtration and washed with ether, and the filtrate was evaporated to dryness. The residue was subjected to column chromatography to give the pure product 11.

1H NMR spectra of compounds 11 showed doubled singlets of methyl groups connected with nitrogen atoms and derived from acetyl or tert-butoxycarbonyl moieties. This fact may indicate that amides 11 coexist as mixtures of rotamers.[23]

N-Methyl-N-[2-(1-oxo-4-phenyl-1H-phthalazin-2-yl)-ethyl]-acetamide (11c)

Yield: 55%; mp 138–140°C; Rf = 0.12 (CH2Cl2-acetone = 9:1); FT-IR (KBr, cm−1) ν: 1652, 1649 (C=O); 1H NMR (200 MHz, CDCl3, ppm, mixture of rotamers) δ: 8.53–8.50 (m, 1H, ArH), 7.81–7.72 (m, 3H, ArH), 7.61–7.50 (m, 5H, ArH), 4.50 (m, 2H, CH2), 3.93–3.77 (m, 2H, CH2), 3.04, 3.02 (2 s, 3H, NMe, two rotamers), 2.02, 1.97 (2 s, 3H, Ac-Me, two rotamers); 13C NMR (50 MHz, CDCl3, ppm, mixture of rotamers) δ: 171.1, 170.9, 159.4, 159.3, 147.8, 147.1, 135.1, 134.8, 133.1, 132.8, 131.7, 131.3, 129.4, 129.3, 129.0, 128.7, 128.6, 127.1, 126.7, 49.0, 48.6, 46.2, 36.7, 33.5, 21.7, 20.9. Anal. calcd. for C19H19N3O2: C, 71.01; H, 5.96; N, 13.07%. Found: C, 70.88; H, 5.99; N, 12.81%.

General Procedure for Preparation of 2-[(Methylamino)ethyl]-2H-phthalazin-1-ones 10

Method A: Hydrolysis of benzenesulfonamides 9. The benzenesulfonamide 9 (0.0106 mol) and H2SO4 (98%, 0.0318 mol) were heated up to 100–110°C over a period of 6 h. After this time the reaction mixture was cooled to ambient temperature, alkalized with 20% aqueous solution of NaOH, and next extracted with
CH$_2$Cl$_2$ (3 x 30 ml). The combined extracts were dried over MgSO$_4$ and concentrated to dryness. The amine was separated by column chromatography.

**Method B: Hydrolysis of tert-butyl methyl[2-(1-oxo-1H-phthalazin-2-yl)ethyl]-carbamates 11.** Carbamate 11 (0.00275 mol) was added to a solution of HCl$_{aq}$ (20%, 36 ml). The mixture was stirred for 30 h at room temperature. Next reaction mixture was alkalinized with 20% aqueous solution of NaOH and extracted with CH$_2$Cl$_2$ (3 x 50 ml). The combined extracts were dried over MgSO$_4$ and concentrated under vacuum. The amine was isolated by column chromatography.

In the case of amines 10 FTIR spectra showed NH bands at $\approx$3320 cm$^{-1}$ and strong C=O bands at 1652 cm$^{-1}$. In the $^1$H NMR spectra of amines 10 (Scheme 3) the signals of the 2-(methylamino)ethyl moiety were displayed as two triplets at $\approx$4.42 and $\approx$3.11 ppm corresponding to CH$_2$ protons of ethylene chain, whereas the protons of NMe and NH groups exhibited as two singlets between 1.52 and 2.51 ppm.

**2-[2-(Methylamino)-ethyl]-4-phenyl-2H-phthalazin-1-one (10c).** Yield: 56% (method A); mp 96–98°C; R$_f$=0.01 (AcOEt–MeOH = 1:1 next MeOH); FT-IR (KBr, cm$^{-1}$) $\nu$: 1652 (C=O), 3332 (NH). $^1$H NMR (200 MHz, CDCl$_3$, ppm) $\delta$: 8.57–8.53 (m, 1H, ArH), 7.82–7.76 (m, 3H, ArH), 7.62–7.53 (m, 6H, ArH), 4.49 (t, 2H, CH$_2$, $J$=6.1 Hz), 3.16 (t, 2H, CH$_2$, $J$=6.1 Hz), 2.51 (s, 3H, NMe), 2.29 (s, 1H, NH); $^{13}$C NMR (50 MHz, CDCl$_3$, ppm) $\delta$: 159.2, 146.9, 135.0, 132.6, 131.2, 129.3, 128.9, 128.4, 127.0, 126.5, 50.3, 50.2, 36.1. Anal. calcd. for (C$_{17}$H$_{17}$N$_3$O): C, 73.10; H, 6.13; N, 15.04%. Found: C, 73.11; H, 5.98; N, 15.11%.

**6-Methoxy-2-[2-(methylamino)-ethyl]-4-(pyridin-2-yl)-2H-phthalazin-1-one (10d).** Yield: 55% (method B); mp 94–96°C; R$_f$=0.0 (AcOEt next MeOH); FT-IR (KBr, cm$^{-1}$) $\nu$: 1652 (C=O), 3316 (NH); $^1$H NMR (200 MHz, CDCl$_3$, ppm) $\delta$: 8.75–7.24 (m, 1H, ArH), 8.42 (d, 1H, ArH, $J$=8.8 Hz), 7.95–7.86 (m, 3H, ArH), 7.42–7.28 (m, 2H, ArH), 4.44 (t, 2H, CH$_2$, $J$=6.1 Hz), 3.88 (s, 3H, OMe), 3.10 (t, 2H, CH$_2$, $J$=6.1 Hz), 2.47 (s, 3H, NMe), 1.52 (brs, 1H, NH); $^{13}$C NMR (50 MHz, CDCl$_3$, ppm) $\delta$: 162.9, 159.3, 154.9, 148.4, 143.3, 137.1, 130.4, 128.9, 124.2, 123.4, 121.9, 120.2, 108.6, 55.5, 50.3, 50.2, 36.0. Anal. calcd. for (C$_{17}$H$_{18}$N$_3$O$_2$): C, 65.79; H, 5.85; N, 18.05%. Found: C, 65.52; H, 5.78; N, 17.93%.

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**SUPPORTING INFORMATION**

Full experimental details, $^1$H and $^{13}$C NMR, and IR spectra can be accessed on the publisher’s website.
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