Application of Organolithium and Related Reagents in Synthesis; Part 26.[1] Synthetic Strategies Based on Directed *ortho*- Metalation: Synthesis of 4-Methyl-2*H*-phthalazin-1-ones

Jan Epsztajn,* Zbigniew Malinowski, Jacek Z. Brzeziński, Monika Karzatka

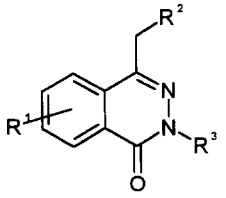
Department of Organic Chemistry, University of Łódź, Narutowicza 68, 90-136 Łódź, Poland
E-mail: epsztajn@krysia.uni.lodz.pl

Received 5 July 2001; revised 28 August 2001

Abstract: The synthesis of 3-hydroxy-3-methylisoindolin-1-ones **10**, masked *ortho*-acetylated derivatives of anilides, via metalation (BuLi) of the benzanilides **1** and subsequent reaction of the generated bis-lithiated anilides **2** with acetylating agents such as acetic anhydride or ethyl acetate were studied. The 3-hydroxy-3-methylisoindolin-1-ones **10** thus obtained are very sensitive towards dehydration process, which caused their conversion into enamides **11**. Conversion of 3-hydroxy-3-methylisoindolin-1-ones **10** or enamides **11** into the corresponding 4-methyl-2*H*-phthalazin-1-ones **13** by treatment with hydrazine, as a way of regioselctive transformation of the benzoic acids, is also described.

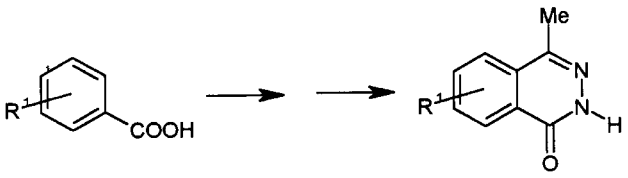
Key words: lithiation, acylations, isoindolinones, phthalazinones

The observed antiallergic[2] and antidiabetic[3] activity of 4-alkyl-2*H*-phthalazin-1-ones derivatives of type **A** has promoted a widespread interest in their synthesis. In particular, our attention was focused on obtaining a general synthetic methodology for 4-methyl-2*H*-phthalazin-1-ones **C** as useful starting materials for **A** (Scheme 1).



A

R^1= H, OMe, Cl
R^2= alkyl, heteroaryl, -COOH
R^3= -CH_2-heteroaryl, -CH_2-heterocyclic



B **C**

Scheme 1

The available methods reported for the preparation of phthalazin-1-ones generally require reaction of *ortho*-carbonylated carboxylic acids[4–7] or their amides[8–10] with hydrazine. Therefore, the current interest is centred on discovering a regiospecific synthetic methodology for the *ortho*-acetylated aromatic carboxylic acids or their derivatives, as starting materials for phthalazin-1-ones **C**. Available methods for the preparation of *ortho*-acetylated aromatic carboxylic acids generally require one of the following techniques. The most common approach involves the Friedel–Crafts reaction, which is usually effected under harsh conditions and does not often proceed with a desired positional specificity.[11] Alternatively, the desired compounds are synthesised via acetylation of aromatic or heteroaromatic zinc, manganese, magnesium, or tin derivatives predominantly by acid chlorides applying the palladium cross-coupling process.[12–20] These systems may be also prepared by the reaction of appropriate halogenated aromatics with (ethoxyvinyl)tributyltin derivatives in the presence of palladium catalyst.[21–23] The most attractive route so far reported to *ortho*-acetylated aromatic carboxylic acids is a directed *ortho*-lithiation of 2-(4-methoxy-3-methylphenyl)-4,4-dimethyl-4,5-dihydrooxazole[24] at the position 6 of benzene ring and reaction with acetic anhydride or *N*-allylbenzamide[25] followed by treatment with *N*-methoxy-*N*-methylacetamide. However, the examples described relate only to specific instances. In a series of recent studies we have reported[9,10,26–28] that the secondary carboxamides moiety namely *N*-phenylamides (anilides) provide an excellent possibility for the regiospecific *ortho*-lithiation and subsequent electrophilic substitution of the aromatic ring, including benzoylation.

Our aim was to extend the scope of this general procedure to the synthesis of new 4-methyl-2*H*-phthalazin-1-ones **C** and we report here the results obtained starting with a series of *N*-phenylbenzoic acid amides (benzanilides) **1**. The route described provides an efficient and general synthetic sequence for the transformation of benzoic acids **B** into 4-methyl-2*H*-phthalazin-1-ones **C** in a two-step protocol starting from benzoic acid anilides **1**.

For this purpose, it appeared necessary to undertake studies which are concerned with the reaction of bis-(*N*- and *C*-*ortho*-lithiated) anilides with acetylating agents. To this

Synthesis 2001, No. 14, 26 10 2001. Article Identifier:
1437-210X,E;2001,0,14,2085,2090,ftx,en;E04501SS.pdf.

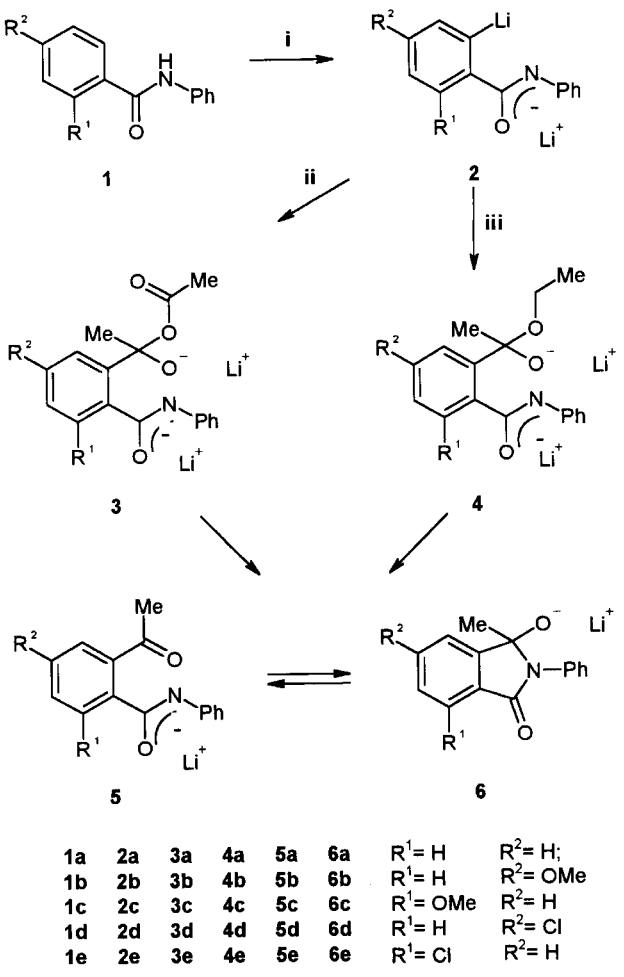
ISSN 0039-7881

end, bis-(*N*- and *C*-*ortho*-lithiated) anilides **2** were efficiently generated upon the treatment of anilides **1** with 2.1 mol equivalents of butyllithium in THF[9,10,26–28] (Scheme 2).

Since the initial report of Nahm and Weinreb[29] on the use of *N*-methoxy-*N*-methylamides as carbonyl equivalents, this acetylating agent has gained tremendous popularity.[30] Hence, at first the bis-lithiated anilides **2** were subjected to reaction with *N*-methoxy-*N*-methylacetamide. Unexpectedly, instead of an effective *ortho*-*C*-acetylation of the anilides a complex mixture was obtained, in which the desired product was present but in a low yield, as was determined by ^{1}H NMR spectroscopy.

It has been suggested[31] that the addition of acetic anhydride to Grignard reagents at low temperature results in the formation of appropriate acetylated derivatives.

Therefore, acetic anhydride was reacted with bis-lithiated anilides **2** which gave new products. However, the compounds formed appeared to be different from the expected bis-acetylated species **7** or **8** (Figure). The ^{13}C NMR spectra of the products from **2a** and **2b** lacked a ketonic carbonyl signal, but it exhibited peaks at δ = 94.5, 50.4, 24.2 and 94.0, 50.3, 24.2, which are appropriate for compounds **9a** and **9b**, respectively. The peaks of the ^{13}C NMR spectrum at δ ≈ 90 are characteristic for a carbon atom at 3 of the 3-hydroxyisoindolin-1-ones.[10,32] The peaks at δ ≈ 50 and ≈ 25 are carbon atom resonances, which are assigned to methoxy and methyl groups. The formation of methoxy derivatives **9** is most probably due to the instability of adducts **3**, which undergo elimination of lithium acetate and lead to the corresponding **5** ⇆ **6** keto-lactol type tautomeric mixture (Scheme 2). Then the lactol-lithium salts **6** reacted with acetic anhydride (excess) to give *O*-acetylated derivatives **8**, which in the presence of the lithium methoxide (methanol quench) produced 3-methoxy-3-methylisoindolin-1-ones **9**.



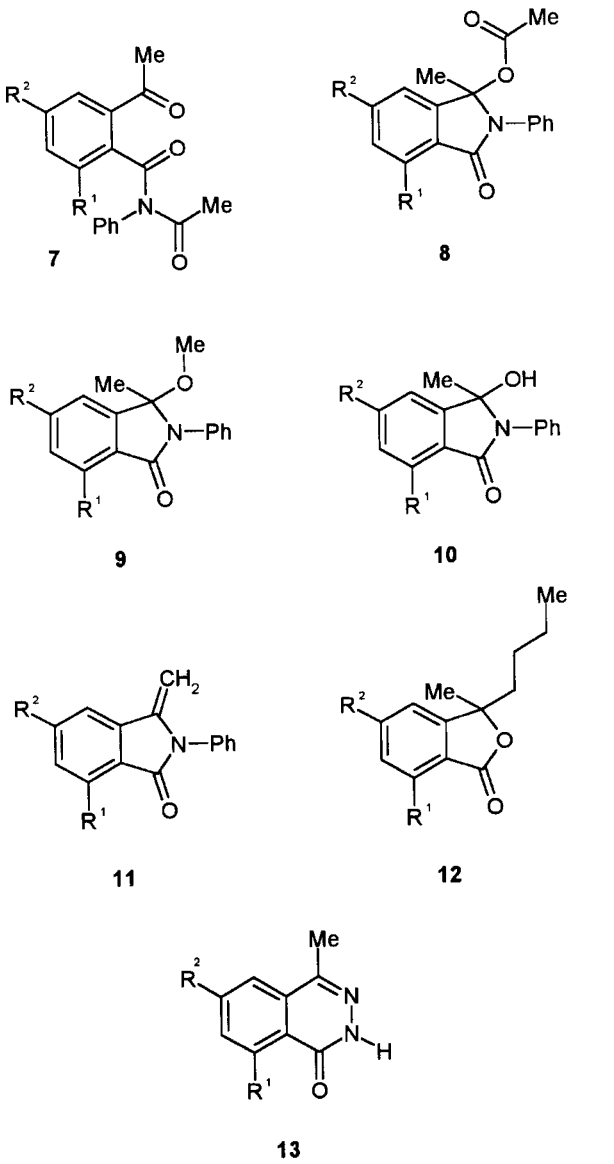
Scheme 2 *Reagents and conditions*: i: a. BuLi, hexanes–THF, –78 °C, 0.5 h; b. 0 °C, 0.5 h; ii: Ac_2O, –78 °C; iii: EtOAc, –78 °C

On the other hand, if water was used for quenching in the reaction of the bis-lithiated anilides **2** with acetic anhydride, the corresponding acetylated derivatives **8** formed upon hydrolytic workup were converted spontaneously into 3-hydroxy-3-methylisoindolin-1-ones **10**, as the stable tautomeric form of *ortho*-acetylated anilides. The products were accompanied by their dehydrated derivatives **11**, as determined by ^{1}H NMR spectroscopy of the crude materials. This elimination is probably due to the acidic quenching conditions. It was observed that the ratio of compounds **10**:**11** depended upon the position and nature of substituents at the aromatic ring. In the case of the anilide **1d** the sole product appeared to be enamide **11b**. Therefore, it can be concluded that the formed isoindolin-1-ones **10** appeared to be very sensitive towards even weak acids, which is responsible for their conversion into enamides **11**. For example, attempted crystallization of isoindolin-1-one **10c** from ethyl acetate caused elimination of water and gave enamide **11a**.

Our recent observation that the reaction of bis-lithiated anilides **2** reacted with aromatic carboxylic acids esters[10,26–28] readily to give the 3-aryl-3-hydroxy-2-phenylizoindolin-1-ones inspired us to test ethyl acetate as an acetylating agent. The treatment of bis-lithiated species **2** with the ethyl acetate afforded the corresponding acetylated derivatives, which spontaneously cyclized to the 3-hydroxy-3-methylisoindolin-1-ones **10**.

In the experiments, in which for the initial lithiation a 5–10% excess of butyllithium was used, the formed 3-hydroxy-3-methylisoindolin-1-ones **10** were accompanied by phthalides **12** (≈5%) resulting from the addition of the lithiating agent to compound **5**. This suggests that in both cases adducts **3** as well as **4** are unstable and eliminate lithium acetate or the lithium ethoxide, leading to the **5** ⇆ **6** keto-lactol tautomeric mixture, respectively. In order to prevent the formation of phthalides **12**, an excess of anilides **1** in the lithiation process appeared to be crucial.

Finally, in order to achieve the synthesis of 4-methylphthalazin-1-ones **13**, the reaction of 3-hydroxyisoindolin-1-ones with the hydrazine hydrate was undertaken. Thus, when the isoindolin-1-ones **10** were treated with hy-



7a	**8a**	**9a**	**10a**		**12a**	**13a**	R^1= H	R^2= H
7b	**8b**	**9b**	**10b**		**12b**	**13b**	R^1= H	R^2= OMe
7c	**8c**		**10c**	**11a**	**12c**		R^1= OMe	R^2= H
			10d	**11b**		**13c**	R^1= H	R^2= Cl
			10e				R^1= Cl	R^2= H

Figure

drazine hydrate in boiling propan-1-ol or acetic acid, the desired phthalazin-1-ones **13** were obtained.

An alternative route to phthalazin-1-ones may be envisaged by the addition of hydrazine to the enamide carbon–carbon double bond of 3-methylene-2,3-dihydro-1*H*-isoindolin-1-ones followed by ring opening and ring closure to afford phthalazin-1-ones, as was recently suggested in the mechanistic discussion concerning the conversion of 2,3-dihydrooxazolate[2,3-*a*]isoindole into the phthalazinones.[33] Indeed reaction of enamides **11** with hydrazine in boiling acetic acid furnished the desired phthalazin-1-ones **13**.

The described methodology for the *ortho*-acetylation of secondary benzamides **1** shows a considerable versatility for the regiospecific synthesis of 3-hydroxy-3-methylisoindolin-1-ones **10** as masked *ortho*-acetylated aromatic carboxanilides. This, coupled with an effective conversion of 3-hydroxy-3-methylisoindolin-1-ones **10** or their corresponding enamides **11** into the corresponding 4-methyl-2*H*-phthalazin-1-ones should allow access to a wide variety of 2*H*-phthalazin-1-ones derivatives.

Melting points were determined using 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 TMS used as an internal reference. A Zeiss-Jena Specord 71-IR spectrometer was used for the IR spectra. The analytical TLC tests were carried out on Merck silica gel plates (Kieselgel 60 F_{254}, layer thickness 0.2 mm) and the spots were visualised using UV lamp. Column chromatography purifications were performed on Merck silica gel (Silica gel 60 (0.063–0.100 mm) using 25g of silica gel per 1g of the purified material. BuLi, solution in hexanes (Aldrich) was titrated each time before use. Hydrazine monohydrate (98%) (Aldrich) was used without further purification. EtOAc (POCh, Poland) and Ac_2O (POCh, Poland) were distilled before use. Anilides **1** are known compounds and were prepared by a standard method.

Bis-lithiated Anilides; General Procedures for Methods A and B

To a stirred solution of **1** (0.02 mol) in THF (90 mL) at –78 °C under argon was added dropwise a solution of BuLi in hexanes (Method A, 0.042 mol), (Method B, 0.036 mol). The mixture was held at –78 °C for 0.5 h, then the temperature was allowed to rise to 0 °C and was kept at this temperature for 0.5 h. This solution of lithiated species was used for reactions at –78 °C with acetylating agents (Ac_2O or EtOAc).

Reactions of Bis-(*ortho*-lithiated) Anilides 2 with Acetylating Reagents Acetic Anhydride (Procedure A) and Ethyl Acetate (Procedure B)

Procedure A: A solution of the bis-lithiated anilide **2** (Method A) at –78 °C under argon was treated with a solution of Ac_2O (0.066 mol) in THF (20 mL). After 0.5 h at –78 °C, the reaction mixture was warmed to r.t. over a 2 h period. To this mixture, MeOH (60 mL) or H_2O (70 mL) was added, the solution was stirred for 0.5 h, and evaporeted to dryness under reduced pressure. H_2O (80 mL) and $CHCl_3$ (100 mL) were added to the residue and neutralized with solid $NaHCO_3$. The H_2O layer was separated and extracted with $CHCl_3$ (3×50 mL). The combined extracts were dried ($MgSO_4$) and concentrated to dryness, and the residue was subjected to column chromatography to give the following compounds: a) 3-methoxy-3-methyl-1*H*-isoindolin-1-ones **9** and unreacted anilides **1** (MeOH quenches); and b) 3-hydroxy-3-methyl-1*H*-isoindolin-1-ones **10** and 3-methylene-1*H*-isoindolin-1-ones **11** and unreacted anilides **1** (H_2O quenches).

2,3-Dihydro-3-methoxy-3-methyl-2-phenyl-1*H*-isoindolin-1-one (9a)

Yield: 40%; eluent: benzene–$CHCl_3$ (6:1); R_f 0.05; mp 167–169 °C (needles from MeOH–H_2O, 1:1).

IR ($CHCl_3$): 1690 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 7.91–7.95 (m, 1 H, ArH), 7.41–7.71 (m, 7 H, ArH), 7.26–7.35 (m, 1 H, ArH), 3.00 (s, 3 H, OCH_3), 1.64 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 166.9 (C=O), 144.3, 135.9, 132.8, 131.7, 129.8, 129.0, 126.7, 125.6, 123.9, 121.9, 94.5, 50.4, 24.2.

Anal. Calcd for $C_{16}H_{15}NO_2$: C 75.87; H 5.97; N 5.53. Found: C 75.79; H 5.66; N 5.20.

3-Dihydro 3,5-dimethoxy-3-methyl-2-phenyl-1*H*-isoindolin-1-one (9b)
Yield: 37%; eluent: benzene–$CHCl_3$ (6:1); R_f 0.15; mp 146–149 °C (needles from MeOH–H_2O, 1:1).

IR ($CHCl_3$): 1700 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 7.84 (d, 1 H, 7 ArH, *J* = 8.4 Hz), 7.40–7.57 (m, 4 H, C_6H_5), 7.24–7.32 (m, 1 H, C_6H_5), 6.96–7.09 (m, 2 H, ArH), 3.92 (s, 3 H, OCH_3), 3.02 (s, 3 H, OCH_3), 1.61 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$) δ = 166.8 (C=O), 163.9, 146.8, 136.1, 129.0, 126.4, 125.5, 124.1, 116.2, 106.6, 94.0, 55.8, 50.3, 24.2.

Anal. Cald for $C_{17}H_{17}NO_3$: C 72.07; H 6.05; N 4.94. Found: C 71.96; H 5.90; N 4.78.

2,3-Dihydro-3-hydroxy-3-methyl-2-phenyl-1*H*-isoindolin-1-one (10a)
Yield: 36%; eluent: benzene–EtOAc (6:1); R_f 0.1; mp 181–186 °C (needles from EtOAc).

IR (KBr): 1675 (C=O), 2800–3600 cm^{-1} (O–H).

^{1}H NMR (DMSO-d_6): δ = 7.69–7.77 (m, 3 H, ArH), 7.42–7.63 (m, 4 H, C_6H_5), 7.31–7.40 (m, 1 H, C_6H_5), 6.80 (s, 1 H, OH), 1.53 (s, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 165.6 (C=O), 149.2, 136.2, 133.0, 130.0, 129.5, 128.9, 127.9, 127.1, 123.0, 122.7, 89.8, 25.1.

Anal. Calcd for $C_{15}H_{13}NO_2$: C 75.30; H 5.48; N 5.85. Found: C 75.12; H 5.48; N 5.91.

5-Chloro-2,3-dihydro-3-methylene-2-phenyl-1*H*-isoindolin-1-one (11b)
Yield: 40%; mp 167.5–170 °C (needles from EtOAc).

IR ($CHCl_3$): 1701 cm^{-1} (C=O).

^{1}H NMR (DMSO-d_6): δ = 8.30 (d, 1 H, 4 ArH, *J* = 1.5 Hz), 7.85 (d, 1 H, 7 ArH, *J* = 8.3 Hz), 7.70 (dd, 1 H, 6 ArH, *J* = 8.1, 1.8 Hz), 7.38–7.62 (m, 5 H, C_6H_5), 5.67 (d, 1 H, CH_2, *J* = 2.2 Hz), 4.78 (dd, 1 H, CH_2, *J* = 2.2 Hz).

^{13}C NMR (DMSO-d_6): δ = 164.5 (C=O), 141.1, 137.6, 133.9, 130.1, 129.2, 128.1, 128.0, 126.7, 124.6, 121.2, 92.8.

Anal. Calcd for $C_{15}H_{10}ClNO$: C 70.46; H 3.94; Cl 13.86; N 5.48. Found: C 70.33; H 3.69; Cl 13.85; N 5.56.

Procedure B: A solution of the bis-lithiated anilide **2** was cannulated into a stirred solution of EtOAc (5g, 0.066 mol) in THF (15 mL) at –78 °C under argon. After 0.5 h at –78 °C, the reaction mixture was warmed to r.t. over 2 h. MeOH (60 mL) was added and the stirring was continued for 0.5 h. The mixture was then evaporated to dryness under reduced pressure. To the resulting residue, H_2O (60 mL) and $CHCl_3$ (100 mL) were added and neutralized with the conc. HCl. The H_2O layer was separated and extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated to dryness. Purification was achieved by column chromatography. In the case of the bis-lithiated anilides **2** (Method A), the residue appeared to be a mixture of similar amounts of starting anilides **1**, 3hydroxy-3-methyl-1*H*-isoindolin-1-ones **10**, and 3-butyl-3-methylphthalides **12** and trace amounts of 3-methylene-1*H*-isoindolin-1-ones **11**, which were identified by ^{1}H NMR of the crude materials. On the other hand, when bis-lithiated anilide **2** was used according to Method B, the residue appeared to be a mixture of starting anilides **1**, 3-hydroxy-3-methyl-1*H*-isoindolin-1-ones **10** and trace amounts of 3-methylene-1*H*-isoindolin-1-ones **11**.

2,3-Dihydro-3-hydroxy-3-methyl-2-phenyl-1H-isoindolin-1-one (10a)
a) Yield: 40% [bis-(*ortho*-lithiated) anilide was generated according to Method A]; eluent: benzene–EtOAc, 6:1, R_f 0.1; mp 181–186 °C (needles from EtOAc).

b) Yield: 42%, [bis-(*ortho*-lithiated) anilide was was generated according to Method B], (eluent: benzene–EtOAc = 6:1, R_f 0.1), mp 181–186 °C (needles from EtOAc.

2,3-Dihydro-3-hydroxy-5-methoxy-3-methyl-2-phenyl-1*H*-isoindolin-1-one (10b)
Yield: 36% [bis-(*ortho*-lithiated) anilide was generated according to Method A]; eluent: benzene–EtOAc (6:1); R_f 0.06; mp 177–182 °C (needles from EtOAc).

IR (KBr): 1680 (C=O), 2800–3600 cm^{-1} (O–H).

^{1}H NMR (DMSO-d_6): δ = 7.65 (d, 1 H, 7 ArH, *J* = 8.3 Hz), 7.41–7.55 (m, 4 H, C_6H_5), 7.28–7.37 (m, 1 H, C_6H_5), 7.25 (d, 1 H, 4 ArH, *J* = 2.2 Hz), 7.09 (dd, 1 H, 6 ArH, *J* = 8.4, 2.3 Hz), 6.78 (s, 1 H, OH), 3.89 (s, 3 H, OCH_3), 1.52 (s, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 165.1 (C=O), 163.1, 151.3, 136.1, 128.5, 127.3, 126.5, 124.3, 122.3, 115.6, 106.8, 89.0, 55.7, 24.8.

Anal. Calcd for $C_{16}H_{15}NO_3$: C 71.36; H 5.61; N 5.20. Found: C 71.39; H 5.63; N 5.27.

2,3-Dihydro-3-hydroxy-7-methoxy-3-methyl-2-phenyl-1*H*-isoindolin-1-one (10c)
Yield: 30% [bis-(*ortho*-lithiated) anilide was generated according to Method A]; eluent: benzene–$CHCl_3$ (6:1); R_f 0.1); mp 137–141 °C (white powder).

IR ($CHCl_3$): 1710 (C=O), 2400–3700 cm^{-1} (O–H).

^{1}H NMR (DMSO-d_6): δ = 7.59–7.68 (m, 1 H, 5 ArH), 7.38–7.50 (m, 4 H, C_6H_5), 7.28–7.36 (m, 1 H, C_6H_5), 7.23 (d, 1 H, 6 ArH, *J* = 7.3 Hz), 7.12 (d, 1 H, 4 ArH, *J* = 8.3 Hz), 6.64 (s, 1 H, OH), 3.88 (s, 3 H, OCH_3), 1.46 (s, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 163.9 (C=O), 156.6, 151.5, 136.2, 134.4, 128.5, 127.7, 126.5, 116.5, 113.9, 112.0, 88.1, 55.6, 24.9.

Attempted crystallization of **10c** from EtOAC led to elimination of H_2O from the material and gave **11a**.

2,3-Dihydro-7-methoxy-3-methylene-2-phenyl-1*H*-isoindolin-1-one (11a)
Yield: 24% [bis-(*ortho*-lithiated) anilide was generated according to Method A]; eluent: benzene–EtOAc (6:1); R_f 0.6; mp 106–110 °C (powder from THF).

IR ($CHCl_3$): 1710 (C=O), 1635 cm^{-1} (C=C).

^{1}H NMR (DMSO-d_6): δ = 7.35–7.70 (m, 7 H, ArH, C_6H_5), 7.21 (d, 1 H, ArH, *J* = 8.1 Hz), 5.43 (d, 1 H, CH_2, *J* = 1.9 Hz), 4.63 (d, 1 H, CH_2, *J* = 1.9 Hz), 3.91 (s, 3 H, OCH_3).

^{13}C NMR (DMSO-d_6): δ = 164.0 (C=O), 156.6, 142.1, 138.1, 134.4, 129.2, 128.7, 128.1, 127.8, 114.7, 112.7, 112.5, 90.2, 55.7.

Anal. Calcd for $C_{16}H_{13}NO_2$: C 76.48; H 5.21; N 5.57. Found: C 76.09; H 4.97; N 5.34.

5-Chloro-2,3-dihydro-3-hydroxy-3-methyl-2-phenyl-1*H*-isoindolin-1-one (10d)
Yield 36% [bis-(*ortho*-lithiated) anilide was generated according to Method A]; mp 160.5–164 °C (plates from EtOH–H_2O, 1:2).

IR (KBr): 1679 (C=O), 3000–3500 cm^{-1} (O–H).

^{1}H NMR (DMSO-d_6): δ = 7.86 (d, 1 H, 4 ArH, *J* = 2.2 Hz), 7.78 (d, 1 H, 7 ArH, *J* = 8.1 Hz), 7.65 (dd, 1 H, 6 ArH, *J* = 8.1, 2.2 Hz), 7.33–7.52 (m, 5 H, C_6H_5), 6.94 (s, 1 H, OH), 1.54 (s, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 164.1 (C=O), 150.4, 137.2, 135.4, 129.3, 128.6, 128.4, 127.3, 126.8, 124.4, 122.4, 89.0, 24.3.

Anal. Calcd for $C_{15}H_{12}ClNO_2$: C 65.82; H 4.42; Cl 12.95; N 5.12. Found: C 65.46; H 4.72; Cl 12.86; N 5.40.

7-Chloro-2,3-dihydro-3-hydroxy-3-methyl-2-phenyl-1*H*-isoindolin-1-one (10e)

Yield: 39% [bis-(*ortho*-lithiated) anilide was generated according to Method A); mp 121–124.5 °C (white powder).

IR (KBr): 1688 (C=O), 3200–3500 cm^{-1} (O–H).

^{1}H NMR (DMSO-d_6): δ = 7.62–7.74 (m, 2 H, ArH), 7.32–7.64 (m, 6 H, ArH), 6.80 (s, 1 H, OH), 1.52 (s, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 163.2 (C=O), 151.9, 135.8, 134.3, 130.8, 129.6, 128.9, 128.2, 127.4, 126.0, 121.5, 88.3, 24.8.

Anal. Calcd for $C_{15}H_{12}ClNO_2$: C 65.82; H 4.42; Cl 12.95; N 5.12. Found: C 65.79; H 4.57; Cl 12.60; N 5.08.

3-Butyl-3-methylphthalide (12a)

Yield: 27% [bis-(*ortho*-lithiated) anilide was generated according to Method A]; eluent: benzene; R_f 0.16; bp 131–133 °C/9 mmHg (Kugelrohr) (pale-yellow oil).

IR (film): 1760 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 7.87 (d, 1 H, 7 ArH, *J* = 7.4 Hz), 7.64–7.72 (m, 1 H, ArH), 7.47–7.57 (m, 1 H, ArH), 7.39 (d, 1 H, 4 ArH, *J* = 7.4 Hz), 1.76–2.14 (m, 2 H, CH_2), 1.65 (s, 3 H, CH_3), 1.12–1.38 (m, 3 H, CH_2), 0.78–1.08 (m, 4 H, CH_3, CH_2).

^{13}C NMR ($CDCl_3$): δ = 170.0 (C=O), 153.9, 134.0, 128.8, 125.9, 125.5, 120.8, 87.7., 39.6, 26.0, 25.5, 22.5, 13.8.

Anal. Calcd for $C_{13}H_{16}O_2$: C 76.44; H 7.90. Found: C 76.42; H 7.95.

3-Butyl-5-methoxy-3-methylphthalide (12b)

Yield: 32%; [bis-(*ortho*-lithiated) anilide was generated according to Method A]; eluent: benzene; R_f 0.05; bp 210–228 °C/0.6 mmHg (Kugelrohr) (pale-yellow oil).

IR (film): 1755 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 7.77 (d, 1 H, 7 ArH, *J* = 8.6 Hz), 7.00 (dd, 1 H, 6 ArH, *J* = 8.5, 2.2 Hz), 6.78 (d, 1 H, 4 ArH, *J* = 2.0 Hz), 3.92 (s, 3 H, OCH_3), 1.74–2.10 (m, 2 H, CH_2), 1.62 (s, 3 H, CH_3), 1.16–1.40 (m, 3 H, CH_2), 0.79–1.02 (m, 4 H, CH_3, CH_2).

^{13}C NMR ($CDCl_3$): δ = 169.9 (C=O), 164.7, 156.7, 127.2, 118.3, 115.8, 105.2, 86.9, 55.8, 39.6, 26.1, 25.5, 22.6, 13.9.

Anal. Calcd for $C_{14}H_{18}O_3$: C 71.77; H 7.74. Found: C 72.02; H 8.06.

3-Butyl-7-methoxy-3-methylphthalide (12c)

Yield: 9% [bis-(*ortho*-lithiated) anilide was generated according to Method A]; eluent: benzene; R_f 0.3; bp 190–198 °C/0.8 mmHg (Kugelrohr) (pale-yellow oil).

IR (thin film): 1760 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 7.60 (dd, 1 H, 5 ArH, *J* = 8.3 Hz), 6.87–6.93 (m, 2 H, 4, 6 ArH), 3.99 (s, 3 H, OCH_3), 1.70–2.10 (m, 2 H, CH_2), 1.60 (s, 3 H, CH_3), 1.15–1.35 (m, 3 H, CH_2), 0.78–1.05 (m, 4 H, CH_3, CH_2).

^{13}C NMR ($CDCl_3$): δ = 168.1 (C=O), 158.4, 156.8, 136.2, 113.4, 112.5, 110.3, 86.3, 55.9, 39.6, 26.2, 25.5, 22.6, 13.9.

Anal. Calcd for $C_{14}H_{18}O_3$: C 71.77; H 7.74. Found: C 71.84; H 7.85.

4-Methyl-2*H*-phthalazin-1-ones 13; General Procedure

A mixture of 3-hydroxy-3-methylisoindolin-1-ones **10** (0.0021 mol) (Method A) or 3methylene-isoindolin-1-ones **11** (0.0021 mol) (Method B) and hydrazine monohydrate (1.6 mL) in propan-1-ol (10 mL) or AcOH (10 mL) was heated under reflux until TLC analysis (EtOAc) indicated the absence of starting material **10** or **11**. After the reaction was complete all the volatile materials were removed under reduced pressure. When propan-1-ol was used as the solvent and H_2O (5 mL) was added to the residue and neutralized with glacial AcOH. The separated product was collected by filtration and purified by recrystallization.

6-Chloro-4-methyl-2*H*-phthalazin-1-one (13c) (One-Pot Procedure)

The crude material from the reaction of metalated 4-chlorobenzanilide **1d**, with EtOAc (Procedure B) [bis-(*ortho*-lithiated) anilide was generated according to Method A] was treated with hydrazine monohydrate (9.5 mL) in AcOH (47 mL) and refluxed until TLC analysis (EtOH) of the reaction mixture indicated the absence of starting material **1d**. All volatile materials were removed under reduced pressure and the crude material was washed with the EtOAc (3 × 15 mL) in order to remove some starting anilide **1d**. The separated product was collected by filtration and purified by recrystallization.

4-Methyl-2*H*-phthalazin-1-one (13a)

Method A, solvent: propan-1-ol; time: 120 h; yield: 75%; mp 227–231 °C (needles from propan-1-ol).

IR ($CHCl_3$): 1670 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 10.86 (s, 1 H, NH), 8.46–8.51 (m, 1 H, ArH), 7.75–7.90 (m, 3 H, ArH), 2.61 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 160.7 (C=O), 144.7, 133.5, 131.4, 130.4, 127.8, 126.9, 125.0, 18.8.

Anal. Calcd for $C_9H_8N_2O$: C 67.49; H 5.03; N 17.49. Found: C 67.24; H 4.62; N 17.65.

6-Methoxy-4-methyl-2*H*-phthalazin-1-one (13b)

Method A, solvent: propan-1-ol; time: 135 h; yield: 70%; mp 247–251 °C (needles from propan-1-ol).

IR ($CHCl_3$): 1660 cm^{-1} (C=O).

^{1}H NMR ($CDCl_3$): δ = 10.28 (s, 1 H, NH), 8.39 (d, 1 H, 8 ArH, *J* = 8.8 Hz), 7.33 (dd, 1 H, 7ArH, *J* = 8.8, 2.4 Hz), 7.09 (d, 1 H, 5 ArH, *J* = 2.4 Hz), 3.98 (s, 3 H, OCH_3), 2.56 (s, 3 H, CH_3).

^{13}C NMR ($CDCl_3$): δ = 163.5 (C=O), 160.3, 144.1, 132.4, 129.1, 121.4, 119.6, 107.0, 55.7, 18.9.

Anal. Calcd for C_{10} $H_{10}N_2O_2$: C 63.15; H 5.30; N 14.73. Found: C 62.95; H 4.95; N 14.80.

6-Chloro-4-methyl-2*H*-phthalazin-1-one (13c)

Method A, solvent: AcOH; time: 22 h; yield: 40%; mp 293.5–297 °C (plates from AcOH–H_2O, 1:1).

Method B, solvent: AcOH; time: 60 h; yield: 30%.

One-pot procedure, time: 45 h; yield: 35%.

IR ($CHCl_3$): 1657 cm^{-1} (C=O).

^{1}H NMR (DMSO-d_6): δ = 12.61 (s, 1 H, NH), 8.27 (d, 1 H, 8 ArH, *J* = 8.6 Hz), 8.04 (d, 1 H, 5 ArH, *J* = 1.8 Hz), 7.93 (dd, 1 H, 7 ArH, *J* = 8.6, 1.8 Hz), 2.52 (s, 3 H, CH_3).

^{13}C NMR (DMSO-d_6): δ = 158.7 (C=O), 142.5, 138.3, 131.6, 131.2, 128.1, 126.0, 125.1, 18.4 (CH_3–C).

Anal. Calcd for $C_9H_7ClN_2O$: C 55.54; H 3.63; Cl 18.22; N 14.39. Found: C 55.20; H 3.67; Cl 18.07; N 14.15.

Acknowledgment

We gratefully acknowledge the support by Grant-in-Aid for Scientific Research from the State Committee for Scientific Research (KBN) and from the University of Łódź.

References

(1) Part 25. Bieniek, A.; Epsztajn, J.; Kowalska, J. A.; Malinowski, Z., Submitted
(2) Kemp, J. C.; Meltzer, E. O.; Orgel, H. A.; Welch, H. J.; Bucholtz, G. A.; Middleton, E. Jr.; Spector, S. L.; Newton, J. J.; Perkach, J. L. Jr. *J. Alergy Clin. Immunol.* **1987**, *79*, 893.
(3) Mylari, B. L.; Larson, E. R.; Beyer, T. A.; Zembrowski, W. T.; Aldinger, C. E.; Dee, M. F.; Sieger, T. W.; Singleton, D. H. *J. Med. Chem.* **1991**, *34*, 108.
(4) Dunet, A.; Willemart, A. *Bull. Soc. Chim. Fr.* **1948**, 108.
(5) Lechat, P. *C. R. Acad. Sci.* **1958**, *246*, 2771.
(6) Sugimoto, A.; Sakamoto, K.; Fujino, Y.; Takashima, Y.; Ishikawa, M. *Chem. Pharm. Bull.* **1985**, *33*, 2809.
(7) Cherkez, S.; Herzig, J.; Yellin, H. *J. Med. Chem.* **1986**, *29*, 947.
(8) Ismai, M. F.; Enayat, E. J.; El-Bassiouny, F. A. A.; Younes, H. A. *Gazz. Chim. Ital.* **1990**, *120*, 677.
(9) Brzeziński, J. Z.; Bzowski, H. B.; Epsztajn, J. *Tetrahedron* **1996**, *52*, 3261.
(10) Brzeziński, J. Z.; Epsztajn, J.; Bakalarz, A. D.; Łajszczak, A.; Malinowski, Z. *Synth. Commun.* **1999**, *29*, 457.
(11) Olah, G. A. *Friedel–Crafts and Related Reactions*; Interscience: New York, **1963**.
(12) Natalini, B.; Mattoli, L.; Pellicciari, R.; Carpenedo, R.; Chiarugi, A.; Moroni, F. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 1451.
(13) Plunket, M. T.; Ellman, T. A. *J. Am. Chem. Soc.* **1995**, *117*, 3306.
(14) Plunkett, M. T.; Ellman, T. A. *J. Org. Chem.* **1995**, *60*, 6006.
(15) Evans, P. A.; Nelso, J. D.; Stanley, A. L. *J. Org. Chem.* **1995**, *60*, 2298.
(16) Yamamoto, Y.; Tanaka, T.; Queki, H.; Miyakawa, M.; Morita, Y. *Heterocycles* **1995**, *41*, 817.
(17) Klement, S.; Standtmžler, H.; Knochel, P.; Caicz, G. *Tetrahedron Lett.* **1997**, *38*, 1927; and references cited therein.
(18) Angle, S. R.; Henry, R. H. *J. Org. Chem.* **1997**, *62*, 8549.
(19) Maeda, H.; Okamoto, J.; Ohmori, H. *Tetraheron Lett.* **1996**, *27*, 5381.
(20) Rieke, R. D.; Kim, S. H.; Wu, X. *J. Org. Chem.* **1997**, *62*, 6921.
(21) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623; and refences cited therein.
(22) Miki, Y.; Tada, Y.; Yanase, N.; Hachiken, H.; Matsushita, K. *Tetrahedron Lett.* **1996**, *37*, 7753.
(23) Johansson, G.; Sundquist, St.; Nordvall, G.; Nilsson, B. N.; Brisander, M.; Nilverbrant, L.; Hacksell, U. *J. Med. Chem.* **1997**, *40*, 3804.
(24) Smith, A. B.; Schow, S. R.; Bloom, T. D.; Thompson, A. S.; Winzenberg, K. N. *J. Am. Chem. Soc.* **1982**, *104*, 4015.
(25) Fisher, L. E.; Muchowski, J. M.; Clarck, R. D. *J. Org. Chem.* **1992**, *57*, 2700.
(26) Epsztajn, J.; Jóźwiak, A.; Czech, K.; Szcześniak, A. K. *Monatsh. Chem.* **1990**, *121*, 909.
(27) Epsztajn, J.; Jóźwiak, A.; Krysiak, J. A. *Tetrahedron* **1994**, *50*, 2907.
(28) Epsźtajn, J.; Jóżwiak, A.; Krysiak, J. K.; Łucka, D. *Tetrahedron* **1996**, *52*, 11025.
(29) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815.
(30) Sibi, M. P. *Org. Prep. Proced. Int.* **1993**, *25*, 15.
(31) March, J. *Advanced Organic Chemistry*, 4 th ed.; Wiley Interscience: New York, **1992**.
(32) Meo, M. K.; Webber, R. K. *J. Chem. Soc., Chem. Commun.* **1990**, 679.
(33) Dekimpe, N.; Virag, M.; Keppens, M.; Stachulski, A. V.; Scheimann, F. *J. Chem. Res. (S)* **1995**, 252.