Russian Journal of Organic Chemistry, Vol. 40, No. 11, 2004, pp. 1702–1704. Translated from Zhurnal Organicheskoi Khimii, Vol. 40, No. 11, 2004, pp. 1746-1748.

SHORT COMMUNICATIONS

Synthesis of Benzo[4,5]imidazo[2,1-*a*]phthalazines

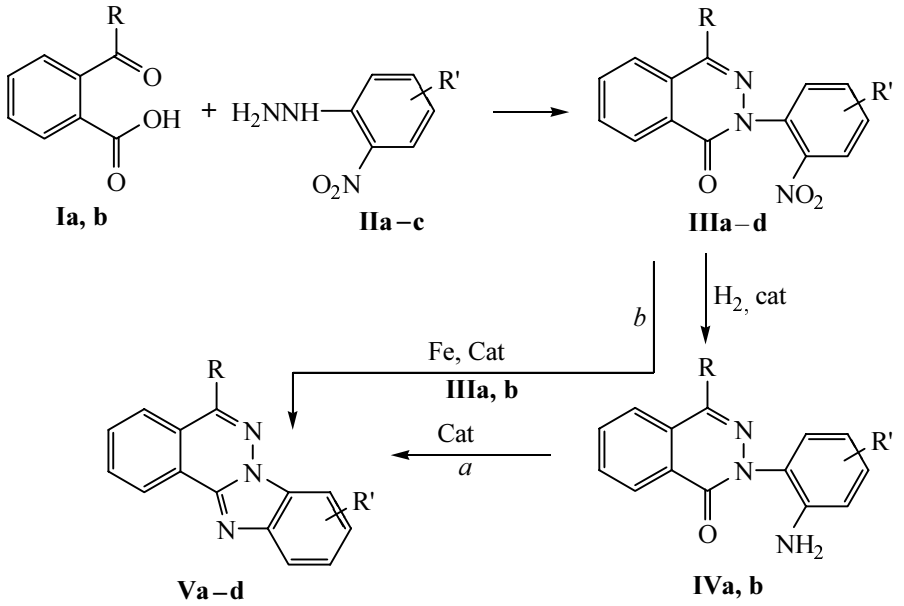
V.A. Kuznetsov, K.M. Shubin, and M.L. Petrov

St. Petersburg State Technological Institute, St. Petersburg, 190013 Russia
e-mail: mlpetrov@tu.spb.ru

Received March 2, 2004

Benzo[4,5]imidazo[2,1-*a*]phthalazines constitute a poorly studied class of angular polycyclic aromatic heterocycles that can be regarded as isoelectronic nitrogen-containing analogs of chrysene. Only twice appeared publications describing preparation and properties of these compounds. First benzo[4,5]imidazo-[2,1-*a*]phthalazines were obtained by cyclization of phthalazinones at heating in sealed tubes [1]. Phthalazinones in their turn were synthesized from *o*-nitroarylhydrazones of 2-carboxybenzaldehyde and 2-carboxyacetophenone. In 1992 an alternative procedure was advanced for preparation of benzo[4,5]imidazo[2,1-*a*]phthalazines from *o*-aminophenols [2]. At the same time the biological activity of this class compounds was discovered.

We developed a new method of synthesis for benzo[4,5]-imidazo[2,1-*a*]phthalazines involving building up in succession of phthalazine and the benzimidazole structure. The synthesis of phthalazinones **III** was performed by cyclization of 2-acylbenzoic acid **I** with *o* nitrophenylhydrazines **II**. One of the most common ways of benzimidazole synthesis involves the use of *o*-arylenediamines with one amino group acylated. The reaction is successful in case the cyclization of the initial compound affords a product of aromatic structure [3]. To prepare such substrate we subjected phthalazinones **III** to catalytic hydrogenetion with gaseous hydrogen aiming at synthesizing aminophthalazinones **IV**. The heating of compounds **IV** in polyphosphoric acid (PPA) afforded benzo[4,5]imidazo-[2,1-*a*]phthalazines (**V**) due to



I, R = CH_3 (**a**), C_6H_5 (b); II, R' = H (a), 4-NO_2 (**b**), 5-Cl (**c**); **III**, R = CH_3: R' = H (**a**), 4-NO_2 (**b**), 5-Cl (**c**); R = C_6H_5, R' = 5-Cl (**d**); **IV**, R = CH_3, R' = 5-Cl (**a**), R = C_6H_5, R' = 5-Cl (**b**); **V**, R = CH_3: R' = H (**a**), 10-NH_2 (**b**), 9-Cl (**c**); R = C_6H_5, R' = 9-Cl (**d**).

1070-4280/04/4011-1702©2004 MAIK "Nauka/Interperiodica"

intramolecular dehydration (procedure *a*) where the phthalazine fragment acted as a cyclic amide. We simplified the synthesis by developing a direct procedure of converting compound **III** into tetracyclic system **V**. This method consists in reduction of nitro compounds **III** with metallic iron in PPA at heating, and the arising amine **IV** is converted into benzoimidazophthalazine (**V**) by increasing the reaction mixture temperature to 130–140°C (procedure *b*). By this method we succeeded in preparation of compounds **Va, b** unpossible to obtain by method *a* because of low solubility of nitro compounds **IIIa, b** and the corresponding amines. Compounds **Vc, d** were synthesized by procedure *b* in higher yields.

The synthetic procedures we developed are a lot simpler than the previous one [2] and also make it possible to synthesize a wide range of benzoimidazophthalazine derivatives in a good yield.

4-Methyl-2-(2-nitrophenyl)-1,2-dihydro-1-phthalazinone (IIIa). A solution of 9.8 g (0.060 mol) of 2-acetylbenzoic acid (**Ia**) and 8.8 g (0.057 mol) of *o*-nitrophenylhydrazine (**IIa**) in a mixture of 80 ml of ethanol and 40 ml of concn. sulfuric acid was boiled for 1.5 h, then it was poured on 300 g of crushed ice, and the separated precipitate was filtered off. On recrystallization from a mixture chloroform–ethanol we obtained 9.6 g (60%) of phthalazinone **IIIa**, mp 195–197°C. ^{1}H NMR spectrum (DMSO), δ, ppm: 2.61 s (CH_3), 7.61–7.78 m ($H^{4'}$, $H^{5'}$), 7.82–8.01 m (H^5, H^6, H^7, $H^{6'}$),* 8.08 d ($H^{3'}$), 8.37 d (H^8). Found, %: C 63.93, 64.21; H 4.02, 4.13; N 14.76, 15.01. $C_{15}H_{11}N_3O_3$. Calculated, %: C 64.05; H 3.94; N 14.94.

2-(2,4-Dinitrophenyl)-4-methyl-1,2-dihydro-1-phthalazinone (IIIb). Likewise from 9.9 g of compound **Ia** and 11.4 g of 2,4-dinitrophenylhydrazine **IIb** after recrystallization from DMF we obtained 9.9 g (54%) of phthalazinone **IIIb**, mp 244–246°C. ^{1}H NMR spectrum (DMSO), δ, ppm: 2.64 s (CH_3), 7.83–8.18 m (H^5, H^6, H^7, $H^{6'}$), 8.37 d (H^8), 8.70 d ($H^{5'}$), 8.80 s ($H^{3'}$). Found, %: C 55.13, 55.31; H 3.04, 3.29; N 17.19, 17.41. $C_{15}H_{10}N_4O_5$. Calculated, %: C 55.22; H 3.09; N 17.17.

4-Methyl-2-(2-nitro-5-chlorophenyl)-1,2-dihydro-1-phthalazinone (IIIc). From 9.8 g of compound **Ia** and 10.7 g of 2-nitro-5-chlorophenyl-hydrazine **IIc** after recrystallization from a mixture chloroform–ethanol we obtained 13.5 g (75%) of phthalazinone **IIIc**, mp 168–170°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.63 s (CH_3), 7.52 d ($H^{4'}$), 7.75 s ($H^{6'}$), 7.78–7.99 m (H^5, H^6, H^7), 8.02 d ($H^{3'}$), 8.44 d (H^8). Found, %: C 56.96, 57.18; H 3.29, 3.41; N 13.17, 13.42. $C_{15}H_{10}ClN_3O_3$. Calculated, %: C 57.07; H 3.19; N 13.31.

2-(2-Nitro-5-chlorophenyl)-4-phenyl-1,2-dihydro-1-phthalazinone (IIId). From 13.6 g of 2-benzoyl-benzoic acid (**Ib**) and 10.7 g of 2-nitro-5-chlorophenylhydrazine (**IIc**) after recrystallization from a mixture chloroform –ethanol we obtained 13.7 g (64%) phthalazinone **IIId**, mp 137–139°C. ^{1}H NMR spectrum (DMSO), δ, ppm: 7.52–7.86 m ($H^{4'}$, $H^{6'}$, 4-phenyl), 7.87–8.01 m (H^5, H^6, H^7), 8.19 d ($H^{3'}$), 8.41 t (H^8). Found, %: C 63.47, 63.68; H 3.15, 3.44; N 11.03, 11.37. $C_{20}H_{12}ClN_3O_3$. Calculated, %: C 63.59; H 3.20; N 11.12.

2-(2-Amino-5-chlorophenyl)-4-methyl-1,2-dihydro-1-phthalazinone (IVa). A solution of 1.9 g (0.006 mol) of 2-(2-nitro-5-chlorophenyl)-4-methyl-1,2-dihydro-1-phthalazinone (**IIIc**) in 20 ml of THF was subjected to hydrogenation by gaseous hydrogen at atmospheric pressure with constant stirring in the presence of 0.16 g of a catalyst (5% Pd on carbon). After consumption of 370 ml of hydrogen within 6 h the reaction mixture was filtered from the catalyst and evaporated to a volume of 10 ml. Then the residue was diluted with petroleum ether (fraction of bp 40–70°C) to 100 ml. The precipitated reaction product was chromatographically pure and was used without additional purification. We obtained 0.7 g (54%) of aminophthalazinone **IVa**, mp 182–184°C. ^{1}H (DMSO), δ, ppm: 2.59 s (CH_3), 5.04 s (NH_2), 6.81 d ($H^{3'}$), 7.07–7.15 m ($H^{4'}$, $H^{6'}$), 7.80–7.98 m (H^5, H^6, H^7), 8.37 d (H^8). Found, %: C 62.87, 62.99; H 4.24, 4.41; N 14.56, 14.74. $C_{15}H_{12}ClN_3O$. Calculated, %: C 63.05; H 4.23; N 14.71.

2-(2-Amino-5-chlorophenyl)-4-phenyl-1,2-dihydro-1-phthalazinone (IVb). Likewise from 2.3 g of 2-(2-nitro-5-chlorophenyl)-4-phenyl-1,2-dihydro-1-phthalazinone (**IIId**) we obtained 1.9 g (93%) of aminophthalazinone **IVa**, mp 185–187°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 3.99 s (NH_2), 6.80 d ($H^{3'}$), 7.17 d ($H^{4'}$), 7.40 d ($H^{6'}$), 7.45–7.58 m (H^2, H^4, H^6 4-phenyl), 7.59–7.65 m (H^3, H^5 4-phenyl), 7.76–7.86 m (H^5, H^6, H^7), 8.61 t (H^8). Found, %: C 69.13, 69.24; H 3.98, 4.17; N 12.22, 12.37. $C_{20}H_{14}ClN_3O$. Calculated, %: C 69.07; H 4.06; N 12.08.

5-Methylbenzo[4,5]imidazo[2,1-*a*]phthalazine (Va). Procedure *b*. To a solution of 1.25 g (0.005 mol) of 4-methyl-2-(2-nitrophenyl)-1,2-dihydro-1-phthalazinone (**IIIa**) in 20 g of PPA heated to 100°C was added by portions at stirring 1.25 g of iron powder. After all iron

* Here and hereinafter the protons of aryl substituent in position 2 are marked with a dash.

was added the reaction mixture was heated for 15 min to 140°C. On cooling the mixture was diluted with water to a 10-fold volume, alkalinized with aqueous NaOH to strongly alkaline reaction, and reaction products were extracted into chloroform (5×50 ml). The combined extracts were dried with Na_2SO_4, filtered, and evaporated. On recrystallization from a mixture chloroform–ethanol we obtained 0.76 g (65%) of compound **Va**, colorless crystals, mp 159–161°C (publ.: 163°C [1]). ^{1}H NMR spectrum (DMSO), δ, ppm: 2.75 s (CH_3), 7.42 m (H^8, H^9), 7.71–8.02 m (H^2, H^3, H^4, H^7, H^{10}), 8.52 d (H^5). Mass spectrum, *m/z* (I_{rel}, %): M^+ 233 (100). Found, %: C 77.24, 77.45; H 4.54, 4.63; N 18.13, 18.26. $C_{15}H_{11}N_3$. Calculated, %: C 77.23; H 4.75; N 18.01.

5-Methyl-10-aminobenzo[4,5]imidazo[2,1-*a*]-phthalazine (Vb). Likewise from 1.7 g of 2-(2,4-dinitrophenyl)-4-methyl-1,2-dihydro-1-phthalazinone (**IIIb**) and 1.7 g of iron powder after recrystallization from a mixture chloroform–ethanol we obtained 0.73 g (58%) of compound **Vb**, colorless crystals, mp >270°C (decomp.). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.84 s (CH_3), 3.83 s (NH_2), 6.85 d (H^9), 7.21 s (H^7), 7.64–7.96 m (H^2, H^3, H^4), 7.98 d (H^{10}), 8.65 d (H^5). Found, %: C 72.36, 72.59; H 4.54, 4.67; N 22.21, 22.43. $C_{15}H_{12}N_4$. Calculated, %: C 72.56; H 4.87; N 22.57.

5-Methyl-9-chloroObenzo[4,5]imidazo[2,1-*a*]-phthalazine (Vc). (a) In 20 g of PPA 1.4 g (0.005 mol) of 2-(2-amino-5-chlorophenyl)-4-methyl-1,2-dihydro-1-phthalazinone (**IVa**) was heated at 140°C. On cooling the reaction mixture was diluted with water to a 10-fold volume, alkalinized with aqueous NaOH to strongly alkaline reaction, and reaction products were extracted into chloroform (3×30 ml). The combined extracts were dried with Na_2SO_4, filtered, and evaporated. On recrystallization from a mixture chloroform–ethanol we obtained 0.9 g (71%) of compound **Vc**, colorless crystals, mp 180–181°C. ^{1}H NMR spectrum (DMSO), δ, ppm: 2.68 s (CH_3), 7.35 d (H^8), 7.81–8.00 m (H^2, H^3, H^4, H^7, H^{10}), 8.41 d (H^5). Mass spectrum, *m/z* ($I_{Otv.}$, %): M^+ 267 (100). Found, %: C 67.43, 67.56; H 3.39, 3.63; N 15.53, 15.78. $C_{15}H_{10}ClN_3$. Calculated, %: C 67.30; H 3.77; N 15.70.

(b) From 1.6 g (0.005 mol) of 2-(2-nitro-5-chlorophenyl)-4-methyl-1,2-dihydro-1-phthalazinone (**IIIc**) and 1.6 g of iron powder we obtained 0.73 g(58%) of compound **Vc**.

5-Phenyl-9-chloroObenzo[4,5]imidazo[2,1-*a*]-phthalazine (Vd). Procedure (a) . In 15 g of PPA 1.5 g (0.0043 mol) of 2-(2-amino-5-chlorophenyl)-4-phenyl-1,2-dihydro-1-phthalazinone (**IVb**) was heated at 130°C. On cooling the reaction mixture was diluted with water to a 10-fold volume, alkalinized with aqueous NaOH to strongly alkaline reaction, and reaction products were extracted into chloroform (3×30 ml). The combined extracts were dried with Na_2SO_4, filtered, and evaporated. On recrystallization from a mixture chloroform–ethanol we obtained 0.9 g (64%) of compound **Vd**, colorless crystals, mp 223–225°C. ^{1}H NMR spectrum (DMSO), δ, ppm: 7.41 d (H^8), 7.58–8.00 m (H^2, H^3, H^4, H^7, H^{10}), 8.62 d (H^5). Mass spectrum, *m/z* ($I_{rel.}$, %): M^+ 329 (100). Found, %: C 72.58, 72.81; H 3.39, 3.47; N 12.83, 12.91. $C_{20}H_{12}ClN_3$. Calculated, %: C 72.84; H 3.67; N 12.74.

(b) From 1.9 g of 2-(2-nitro-5-chlorophenyl)-4-phenyl-1,2-dihydro-1-phthalazinone (**IIIc**) and 1.9 g of iron powder we obtained 1.1 g (64%) of compound **Vc**.

Melting points were measured on a Boëtius heating block. ^{1}H NMR spectra were registered on spectrometer Bruker AMX-400 (400 MHz), as internal references served signals of residual protons (^{1}H) of deuterated solvents. Mass spectra were recorded on a mass spectrometer Kratos MS 890 at a direct admission of a sample into the ion source, ionizing electrons energy 70 eV, temperature in the ionization chamber 200°C. The reaction progress was monitored by TLC on Silufol UV-254 plates, spots were visualized by UV irradiation. All solvents used in the study were purified and dried by standard procedures.

REFERENCES

1. Rowe, F.M., Adams , D.A.W., Peters, A.T., and Gillam, A.E., *J. Chem. Soc.,* 1937, p. 90.
2. Razvi M. and Ramalingam T., *Indian. J. Chem.* 1992, 31B, p. 788.
3. Grimmett, M.R., *Imidazole and Benzimidazole Synthesis*, Leningrad: Academic Press, 1997, 265 p.