One-Pot Synthesis of 3-Aryl-*s*-triazolo[3,4-*a*]phthalazines by Lead(IV) Acetate Oxidation of *ortho*-Phthalaldehyde Bis-aroylhydrazones

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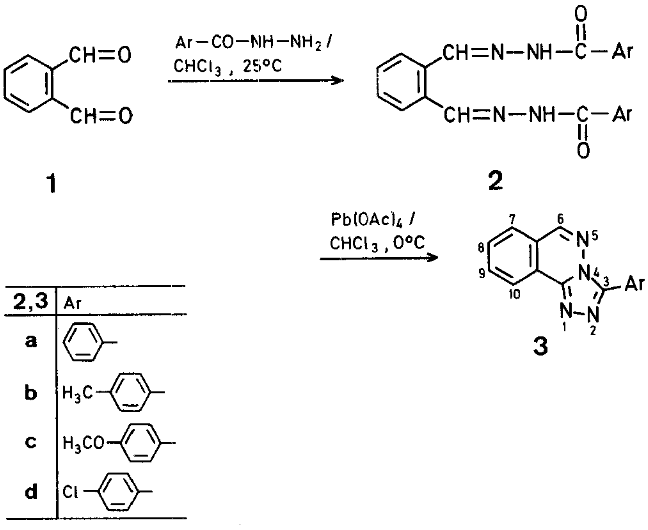
It has recently been found[2] that lead(IV) acetate oxidation of bis-arenesulfonyl-hydrazones of *ortho*-phthalaldehyde gives phthalazine in high yield. In continuation of our work on lead(IV) oxidations of various heteroallylic systems[3] we studied the behaviour of *ortho*-phthalaldehyde bis-aroylhydrazones (**2**). Oxidation of the hydrazones **2** in chloroform at 25 °C with lead(IV) acetate afforded the unexpected 3-aryl-*s*-triazolo[3,4-*a*]phthalazines (**3**) which could be isolated from resinous by-products in moderate yields (9–23%).



Compounds **2** have been prepared from *ortho*-phthalaldehyde (**1**) by reaction with benzoic hydrazides in chloroform at 25 °C. In the I.R. spectra (Nujol), the hydrazones **2** exhibit two bands $\nu = 3200-3400\ \text{cm}^{-1}$ (NH) and a band at $\nu = 1645-1660\ \text{cm}^{-1}$ (C=O). The mass spectra show molecular ions of very low intensities. The ¹H-N.M.R. data (DMSO-d_6) suggest that, similar to the findings in *ortho*-phthalaldehyde bis-arenesulfonylhydrazones[2], the two hydrazone side chains are equivalent. Besides peaks for the aromatic protons, two singlets at $\delta = 8.90-9.08$ (—C<u>H</u>=) and $\delta = 11.72-11.95$ ppm (=N—N<u>H</u>—CO—) are found.

The structural assignment of compounds **3** is based on spectral data. In the I.R. spectra no absorptions for NH and C=O groups are present. The ¹H-N.M.R. spectra show two multiplets centered at $\delta = 7.80-7.90$ (H-7, H-8, H-9) and 8.68–8.73 ppm (H-10), a singlet at $\delta = 8.63-8.70$ ppm (H-6) and the expected pattern for the aromatic protons of the 3-aryl groups. The known 3-(2-carboxyphenyl)-*s*-triazolo[3,4-*a*]phthalazine[4] gives very similar ¹H-N.M.R. data. In the mass spectra the molecular ions represent intensive peaks (often base peaks). Furthermore, peaks belonging to $[M-H]$, $[M-ArCN_2]^{\oplus}$, $[M-ArCN_3]^{\oplus}$, $[Ar-CN]^{\oplus}$, and $Ar^{\oplus}$ ions are found.

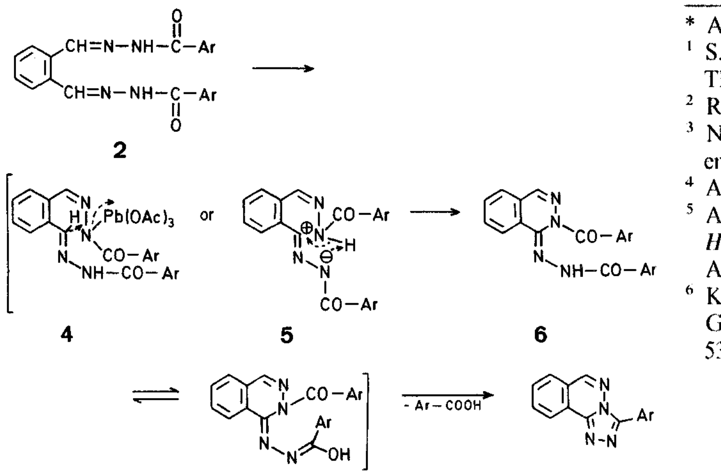
The unexpected oxidation reaction could proceed by one of the following reaction paths.

In agreement with previous observations[2], the action of lead(IV) acetate could give the *N*-metallated intermediate **4** which by cyclization yields **6**. Alternatively, **6** could be formed via oxidation to the corresponding nitrile imine **5**[3] followed by an intramolecular addition step. Finally, the *s*-triazolo ring is created by tautomerization to **7** and elimination of the corresponding benzoic acid.

Table. Compounds **2** and **3** prepared.

Product 2				Product 3			
No.	Yield [%]	m.p. [°C]	Molecular formula[a]	No.	Yield [%]	m.p. [°C]	Molecular formula[a]
2a	67	174–176°	$C_{22}H_{18}N_4O_2$ (370.4)	**3a**	15	215–216°	$C_{15}H_{10}N_4$ (246.3)
2b	83	163–165°	$C_{24}H_{22}N_4O_2$ (398.4)	**3b**	23	222–223°	$C_{16}H_{12}N_4$ (260.3)
2c	90	156–158°	$C_{24}H_{22}N_4O_4$ (430.4)	**3c**	16	203–205°	$C_{16}H_{12}N_4O$ (276.3)
2d	90	183–185°	$C_{22}H_{16}Cl_2N_4O_2$ (439.2)	**3d**	9	228–230°	$C_{15}H_9ClN_4$ (280.7)

[a] The microanalyses showed maximum deviations from the calculated values for C, H, N, ±0.25. Exceptions: **2b**, C – 0.43; **3c**, **3d**, N – 0.38. The spectroscopic data (I.R., N.M.R., M.S.) of all products were in agreement with the proposed structures.



It should be noted that the similar oxidation of *meta*-phthalaldehyde bis-aroylhydrazones produces the expected 1,3-bis[5-aryl-1,3,4-oxadiazol-2-yl]benzenes[1].

s-Triazolo[3,4-*a*]phthalazines show hypotensive activity[5] and several 3-substituted derivatives have been synthesized[5,6] by cyclization of 1-hydrazinophthalazine with aliphatic acids, orthoesters, urea, carbon disulfide, and similar reagents. With the exception of the 3-(2-carboxyphenyl) derivative[4], 3-aryl derivatives have not been obtained previously.

ortho-Phthalaldehyde Bis-aroylhydrazones (2); General Procedure:

A mixture of *ortho*-phthalaldehyde (**1**; 1 molar equivalent) and aroylhydrazine (2.1 molar equivalent) in chloroform (25 ml per mmol **1**) is stirred at 25 °C for 24 h. The precipitated hydrazone **2** is isolated by suction, washed with methanol and recrystallized from methanol (Table).

3-Aryl-*s*-triazolo[3,4-*a*]phthalazines(3); General Procedure:

To a suspension of the hydrazone **2** (10 mmol) in chloroform (80 ml), free from ethanol, a solution of lead(IV) acetate (4.48, 10.1 mmol) in chloroform (80 ml) is added at 25 °C with stirring over a period of 1 h. After further stirring for 2 h, the mixture is poured into water (150 ml). The organic layer is washed with aqueous 10% sodium carbonate (50 ml) and water (50 ml), dried with sodium sulfate, and evaporated in vacuo. By addition of acetone (10 ml) to the residue and leaving the mixture at 25 °C, compound **3** separates as a solid which is crystallized from methanol. Further purification is achieved by sublimation at 185 °C/3 torr and recrystallization from methanol (Table).

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