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PHTHALAZINE DERIVATIVES FROM AROMATIC ALDAZINES

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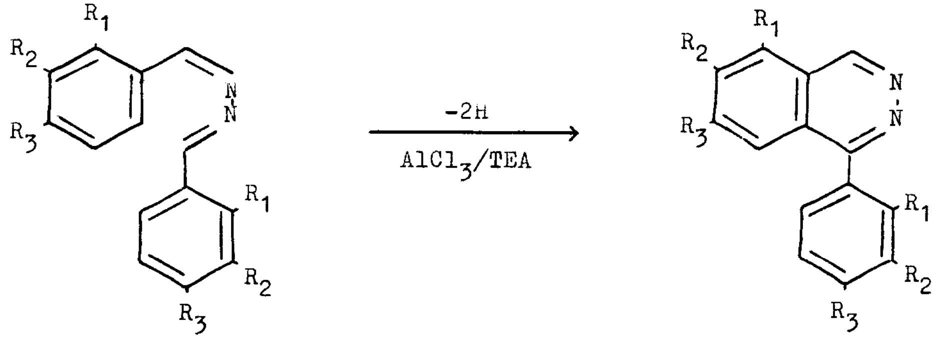
Summary: A Lewis acid mediated synthesis of phthalazine derivatives II and III from aromatic aldazines I is reported.

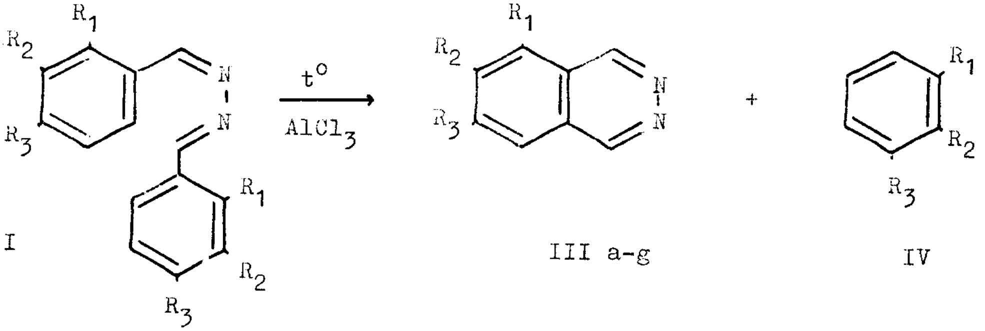
In the present paper we report a new synthesis of 1-arylphthalazine derivatives II from aromatic aldazines I by heating with aluminium chloride/tri - ethylamine(TEA)(molar ratio 2:1) at 170-200°C.



I

II a-h

$AlBr_3$/TEA also proved to be a good reagent, promoting formation of II from I, the yield being up to 70%. We have found that when $AlCl_3$ alone reacts with I (molar ratio $AlCl_3$:I more than 12) mainly elimination of one of the aryl residues occurred as arene or haloarene IV and phthalazine derivatives III are for med unsubstituted in the pyridazine nucleus. 3-Chloro- and 3-methyl- substituted benzaldazines gave mixtures of the corresponding 5- and 6-substituted phthalazines, the ratio being approximately 5:1. From 3-bromobenzaldazine we isolated 6-bromophthalazine.

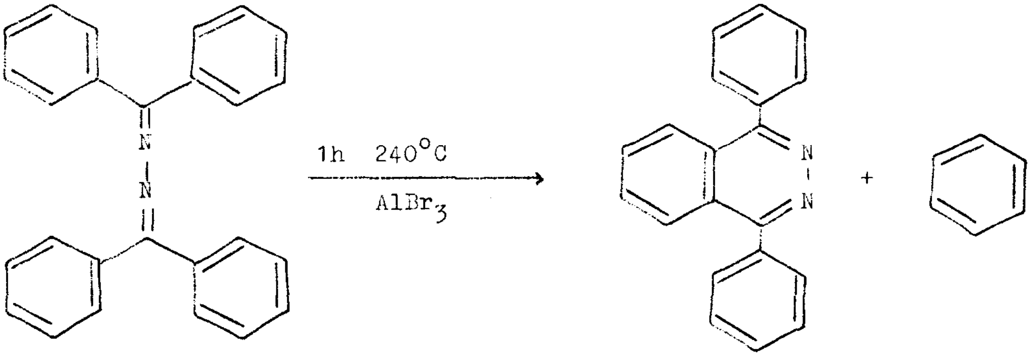


Pure $AlBr_3$, compared with $AlCl_3$ and AlX_3/TEA, occupies intermediate position with regard to the cyclization of I, giving rise both to II and III. In the synthesis of III its addition to $AlCl_3$ is useful as "liquefier" in the temperature range 170-210°C.

II	R_1	R_2	R_3	mp C°(yield %)	
a	H	H	H	149 (1)	63
b	H	H	CH_3	102	68
c	CH_3	H	CH_3	114	60
d	H	H	Cl	193	70
e	F	H	H	107	27
f	H	H	iPr	132	40
g	H	H	Br	208	65
h	Cl	H	H	156	62

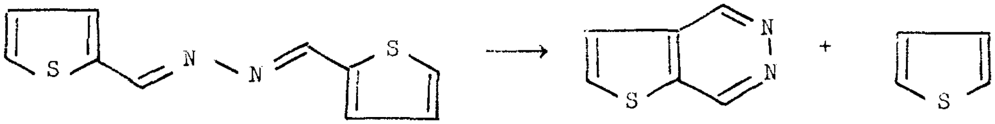
III	R_1	R_2	R_3	mp C°(yield %)	
a	H	H	H	91(2)	43
b	H	H	CH_3	72	18
c	CH_3	H	CH_3	106	65
d	H	H	Cl	139	20
e	H	H	Br	110(3)	35
f	Cl	H	H	128	45
g	H	H	C_6H_5	139(4)	15

The elimination of IV during the synthesis of III seems to be of wider validity since we have further established that a similar process takes place also in the case of benzophenone azine V from which 1,4-diphenylphthalazine VI(5) was synthesised in 60 % yield, with liberation of benzene. All compounds of types II and III are newly synthesised, except IIa, IIIa, IIIe and IIIg. Their structure was elucidated on the basis of elemental microanalysis, nmr, ir, UV and mass spectral data.



V VI

In analogous way thieno/2,3-d/pyridazine VIII was synthesised from thiophene-2-aldehyde azine VII in 40% yield, which might be a synthesis of choice if the necessary thiophene-2,3-dialdehyde used by Robba et al. for the synthesis of the same compound(6) is not at hand.



VII VIII

It should be pointed out however that we were not able to obtain the expected pyrido/2,3-d/pyridazine when the reaction was tried with pyridine-2-aldazine and the starting aldazine was quantitatively recovered.

<u>1-(2,4-Dimethylphenyl)-5,7-dimethylphthalazine IIc</u>

0,53g (2 mmole) 2,4-Dimethylbenzaldazine Ic and 2,0g (15 mmole) $AlCl_3$ were mixed together and 1,0 ml (7,17 mmole) TEA was added, with cooling. After 1 hour at 180-200°C the dark homogeneous reaction mixture was cooled and treated with 30 ml ice water. The resulted suspension was filtered and washed with dilute HCl and the combined filtrate was made alkaline with 15% KOH. The precipitate was collected, dried and recrystallised from n-hexane giving IIc (0,31g, 60%, mp 113-114°C).

The aqueous filtrate after the separation of IIc was extracted with benzene and the solvent distilled off under reduced pressure. The residue gave a negligible amount of crystals (mp 105°C) which were identified as 5,7-dimethylphthalazine IIIc.

$C_{18}H_{18}N_2$, M^+ 262; UV(ethanol) λ max(log e)nm 231(4,83), 287(3,97);

^{1}H nmr, 80 MHz, $\delta^{TMS}_{CDCl_3}$ 2,13(3H,s, o-CH_3), 2,37(6H,s, p-CH_3, 5-CH_3), 2,80 (3H,s, 7-CH_3), 6,90-7,60(5H,m, arom.), 9,65(1H,s, H_4) ppm. Picrate mp 164°C (ethanol).

5,7-Dimethylphthalazine IIIc 0,53g (2 mmole) Ic, 4,0g (30 mmole) $AlCl_3$ and 4,0g (15 mmole) $AlBr_3$ were heated at 185-195°C for 30 min, the reaction mixture treated under cooling with 50 ml water and after addition of 5 ml 5% HCl the filtered solution was made alkaline with 15% KOH and extracted thoroughly with benzene. After evaporation of the organic solvent the crude IIIc crystallised in needles which recrystallised from benzene/n-hexane melted at 105-106°C; yield 0,21g(65%).

$C_{10}H_{10}N_2$, M^+ 158; UV(ethanol) λ max(log e)nm 228(4,85), 276(3,86);

^{1}H nmr, 80 MHz, $\delta^{TMS}_{CDCl_3}$ 2,60(3H,s, 5-CH_3), 2,75(3H,s, 7-CH_3), 7,50(2H, H_6 & H_8), 9,38(1H,s, H_4), 9,58 (1H,s, H_1) ppm. Picrate mp 208°C(ethanol).

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