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RING CONTRACTION SYNTHESIS OF 2,5-DISUBSTITUTED-3-ARYLAMINO-4-CYANOPYRROLES FROM 2,6-DISUBSTITUTED-4-ARYLAMINO-5-CYANOPYRIMIDINES

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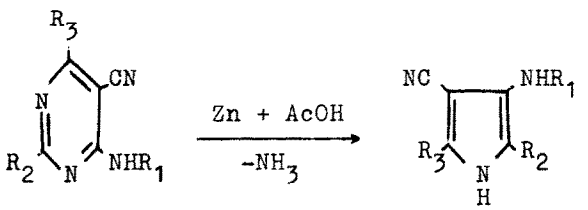
Summary: A method for synthesis of 2,5-disubstituted-3-arylamino-4-cyanopyrroles from newly synthesised 2,6-disubstituted-4-arylamino-5-cyanopyrimidines by treatment with zinc and acetic acid, the yields being up to 80%, is developed.

It has been reported that triphenyl-s-triazine[1] or triphenylthiotriazine[2] undergo ring contraction by treatment with zinc and acetic acid giving triphenylimidazole, resp. triphenylozotriazole. In the pyrimidine series examples of similar ring contraction leading to pyrroles have been observed by T.W.Thompson[3] while attempting to dehalogenate certain 4-chloropyrimidines using zinc and aqueous acetic acid, although it is well known that usually the pyrimidine nucleus remains stable against zinc and acetic acid[4]. In that way Thompson[3] and later Longridge and Thompson[5] have synthesised several arylpyrroles and esters of arylpyrrolylacetic acids.

We now report a method for synthesis of the unknown until now 2,5-disubstituted-3-arylamino-4-cyanopyrroles II through ring contraction of the newly synthesised 2,6-disubstituted-4-arylamino-5-cyanopyrimidines I by treatment with zinc and acetic acid without affecting the cyano group. The synthesis is easy to perform and as a rule the products are obtained satisfactorily pure and with yields reaching up to 80%. Presently the method is successfully applied on over 30 cases, permitting the synthesis of a wide

variety of 3-arylamino-4-cyanopyrroles.



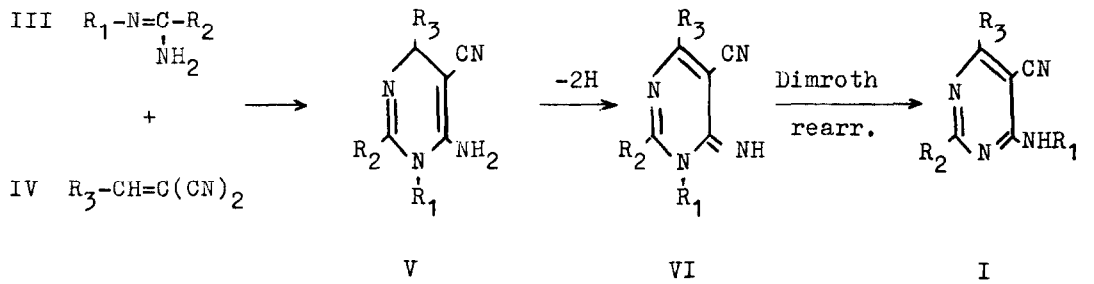
Ia-w IIa-w

	R_1	R_2	R_3	I m.p.C°	(yield %)	II m.p.C°	(yield %)
a	C_6H_5	C_6H_5	C_6H_5	268	(71)	186	(72)
b	C_6H_5	2-$C_{10}H_7$	C_6H_5	303	(68)	210	(65)
c	4-$CH_3C_6H_4$	C_6H_5	C_6H_5	270	(62)	209	(59)
d	C_6H_5	C_6H_5	2-$C_{10}H_7$	245	(66)	201	(67)
e	C_6H_5	C_6H_5	4-$CH_3C_6H_4$	248	(70)	247	(52)
f	C_6H_5	4-$CH_3C_6H_4$	C_6H_5	276	(75)	228	(63)
g	C_6H_5	C_6H_5	4-$CH_3OC_6H_4$	257	(63)	229	(58)
h	C_6H_5	C_6H_5	4-BrC_6H_4	284	(47)	230	(50)
i	C_6H_5	4-$CH_3C_6H_4$	2-$CH_3OC_6H_4$	199	(55)	193	(71)
j	3-ClC_6H_4	C_6H_5	C_6H_5	247	(63)	185	(55)
k	3-ClC_6H_4	C_6H_5	2-$CH_3OC_6H_4$	226	(58)	180	(70)
l	C_6H_5	C_6H_5	3-BrC_6H_4	214	(55)	172	(52)
m	C_6H_5	4-$CH_3OC_6H_4$	C_6H_5	263	(61)	203	(65)
n	4-$CH_3OC_6H_4$	C_6H_5	C_6H_5	284	(58)	204	(61)
o	3-FC_6H_4	C_6H_5	C_6H_5	254	(56)	183	(70)
p	C_6H_5	4-$C_2H_5OC_6H_4$	C_6H_5	257	(48)	214	(75)
q	1-$C_{10}H_7$	C_6H_5	C_6H_5	222	(45)	267	(80)
r	C_6H_5	2-$C_{10}H_7$	2-$C_{10}H_7$	288	(61)	222	(77)
s	C_6H_5	C_6H_5	2-$C_2H_5OC_6H_4$	201	(57)	184	(58)
t	C_6H_5	2-$C_{10}H_7$	4-$CH_3C_6H_4$	295	(62)	267	(65)
u	4-BrC_6H_4	2-$C_{10}H_7$	C_6H_5	326	(56)	211	(70)
v	1-$C_{10}H_7$	C_6H_5	4-$CH_3C_6H_4$	215	(45)	212	(53)
w	3-ClC_6H_4	C_6H_5	2,4-$(CH_3)_2C_6H_3$	217	(30)	186	(63)

The reaction of the 2,6-disubstituted-4-arylamino-5-cyanopyrimidines with zinc and acetic acid is usually carried out by heating for 1-2 hours but it can proceed also at room temperature under stirring overnight. Analytical determinations of ammonia formed during the reaction revealed that the amount of ammonia parallels the pyrrole yield within 3% limit.

The structure II is assigned on the basis of analytical and spectral data and of chemical behaviour as well-on pyrolysis the newly synthesised diphenyl-arylamino-cyanopyrroles gave 2,5-diphenyl-3-cyanopyrrole and the corresponding arylamine, the former one having been identified by comparison with authentic sample obtained according to the procedure described by Henze and Shown jr.[6]

The starting 2,6-disubstituted-4-arylamino-5-cyanopyrimidines were synthesised using a new one pot method developped by us from N-monosubstituted amidines[7,8,9] III and ylidenemalononitriles[10,11] IV (Intermediates V - 2,3,6-trisubstituted-4-amino-5-cyano-3,6-dihydropyrimidines and VI - 2,3,6-trisubstituted-4-imino-5-cyano-3,4-dihydropyrimidines are isolated if the interaction between the N-monosubstituted amidine and ylidenemalononitrile is carried out at low temperature in tetrahydrofuran).Yields up to 75%.



The general procedure for synthesis of 2,5-disubstituted-3-arylamino-4-cyanopyrroles may be demonstrated on the following example:

2,5-Diphenyl-3-anilino-4-cyanopyrrole. 3,48g (10 mmole) 2,6-diphenyl-4-anilino-5-cyanopyrimidine (obtained by melting together equimolar quantities of N-phenylbenzamidine and benzylidenemalononitrile at 110°C for 3 hours) are thoroughly mixed with 4g zinc powder and the mixture is refluxed for 2 hours in 50 ml acetic acid. The hot filtrate is treated with boiling water

until crystallisation begins and the system is allowed to cool to give colourless crystals which melt at 180-182°C; 2,38g (72%). The pure 2,5-diphenyl-3-anilino-4-cyanopyrrole has m.p. 185-186° (from toluene); ms 335(M^+) ; IR(nujol) 3420, 3390, 3280 NH, 2220 CN, cm^{-1}; UV, ethanol, λ max(lg ε) 210 (4,28), 243(4,32), 298(4,32) nm; ^{1}H NMR, 60 MHz, $\delta^{TMS}_{CDCl_3}$ 5,20(1H,s), 7,20 - 7,80(15H,m), 9,00(1H,s).

All newly synthesised compounds are stable in solid state. Boiling with concentrated alkaline hydroxides or hydrochloric acid practically does not affect them.

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