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SYNTHESIS OF TRIAZOLES AND OXADIAZOLES FROM 2-ARYL-3-PHENYL-4-IMINO-5-CYANO-3,4-DIHYDROPYRIMIDINES

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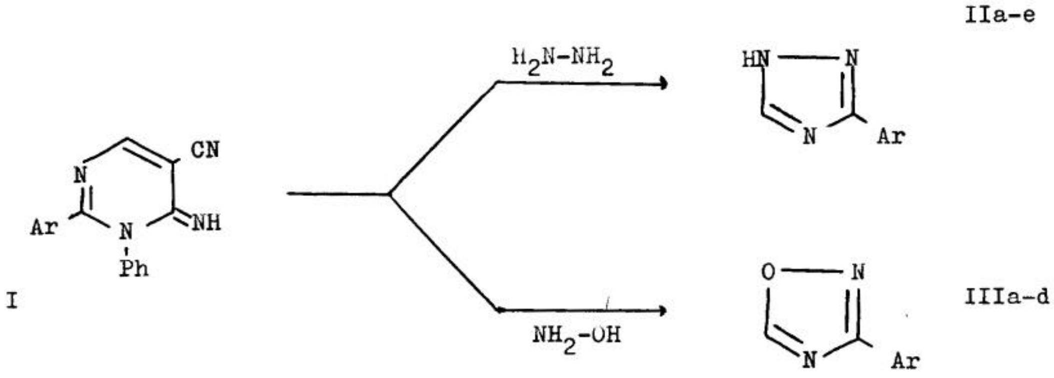
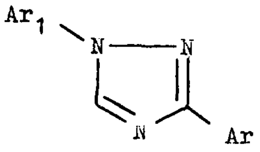
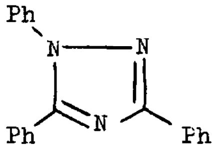
Summary: 2-Aryl-3-phenyl-4-imino-5-cyano-3,4-dihydropyrimidines I were transformed to 1,2,4-triazoles II,IV and 1,2,4-oxadiazoles III by treatment with hydrazine, arylhydrazines or hydroxylamine in yields up to 90%.

In the present paper we report a new synthesis of 3-arylsubstituted 1,2,4-triazoles II and 3-aryl-1,2,4-oxadiazoles III from easy available ⁽¹⁾ 2-aryl-3-phenyl-4-imino-5-cyano-3,4-dihydropyrimidines I by treatment with hydrazine or hydroxylamine at room temperature.



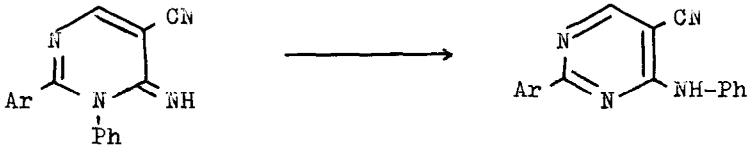
We have found that the reaction takes place when I was stirred for 5-10 min with either hydrazine hydrate or hydroxylamine, to give II or III, in yields up to 90%. If instead of hydrazine hydrate in the reaction with I arylhydrazines were used the isolated product was the corresponding 1,3-diaryl-1,2, 4-triazole IV. In all our experiments III and IV were obtained free from other isomers. This fact shows that the transformation of I into III and IV went regiospecifically.


IVa-h


XI

It should be pointed out that under the conditions tested so far we failed to carry out a similar reaction with guanidine, thiosemicarbazide or ethylenediamine, the only compound isolated in all these cases being a Dimroth rearrangement product - the corresponding 2-aryl-4-anilino-5-cyanopyrimidine V :

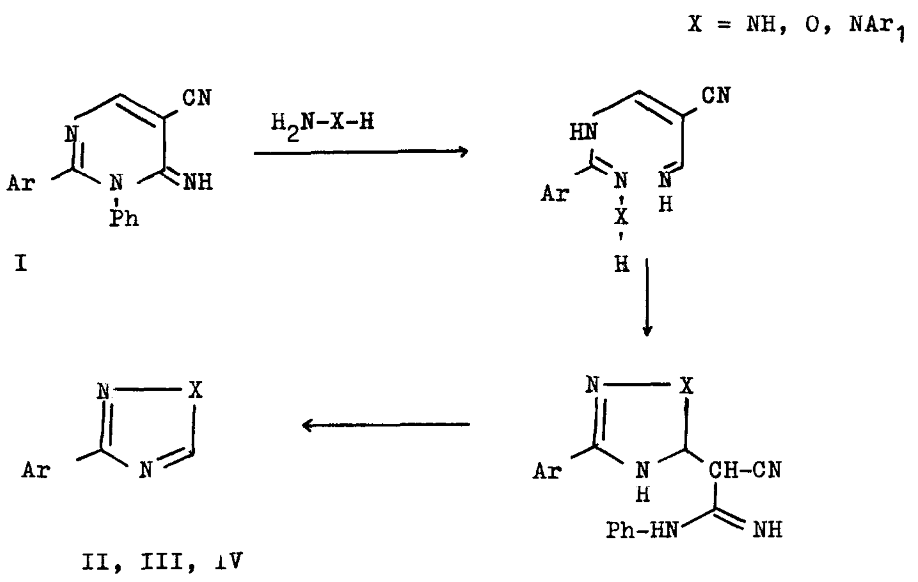
I



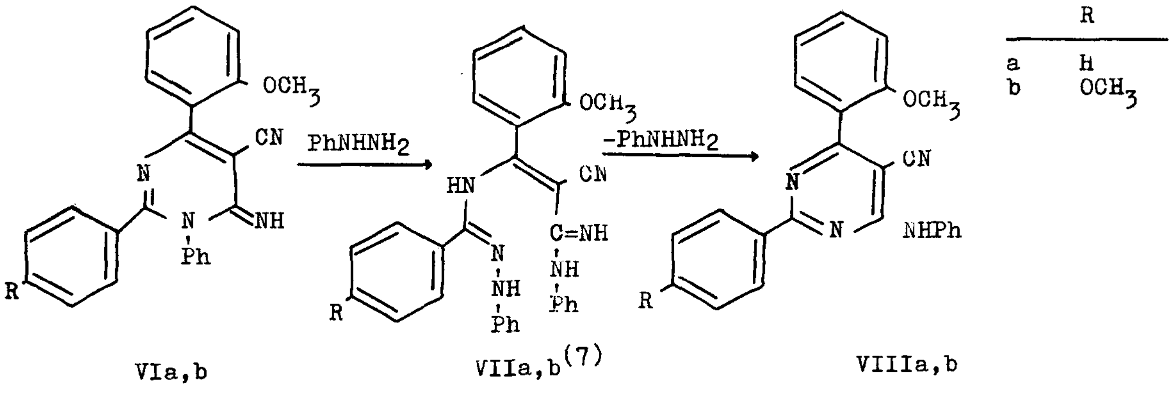
V

II III	Ar	mp C° (bp/mm Hg)	Yield %	IV	Ar_1	Ar	mp C°	Yield %
IIa	C_6H_5	118(2)	80	a	C_6H_5	C_6H_5	83(4)	78
b	$4-CH_3C_6H_4$	174(2)	72	b	C_6H_5	$2-C_4H_3S$	114	80
c	$4-ClC_6H_4$	194(2)	65	c	C_6H_5	$4-ClC_6H_4$	124	87
d	$4-Me_2NC_6H_4$	195	68	d	C_6H_5	$4-CH_3C_6H_4$	71	60
e	$2-C_4H_3S$	119	75	e	C_6H_5	$2-C_{10}H_7$	125	92
IIIa	C_6H_5	(95/10)(3)	90	f	$4-CH_3C_6H_4$	$2-C_{10}H_7$	128	55
b	$4-CH_3C_6H_4$	(115/10)(3)	85	g	$4-CH_3C_6H_4$	$2-C_4H_3S$	84	50
c	$4-ClC_6H_4$	104(3)	75	h	$4-FC_6H_4$	$4-MeOC_6H_4$	128	78
d	$4-Me_2NC_6H_4$	85	75					

The reaction of I with hydrazine, hydroxylamine or Ar_1NHNH_2 proceeds, in our opinion, through a Dimroth type addition of the nucleophile leading to the cleavage of C_2-N_3 bond and followed by cyclization according to the scheme:



Using as model substances VIa and VIb containing an ortho-methoxy-substituted phenyl residue at position 6 (the sterically unhindered 2,6-diphenylated analogue gave 1,3,5-triphenyl-1,2,4-triazole(5) XI) we were able to isolate the intermediate VII in the reaction with $PhNHNH_2$. On boiling in ethanol VII did not give the corresponding 1,3,5-trisubstituted 1,2,4-triazole but gave the normal Dimroth rearrangement product VIII with liberation of $PhNHNH_2$ (6) :



With sterically less bulky nucleophiles like hydrazine and hydroxylamine VI gave the corresponding 3,5-diarylated 1,2,4-triazoles and 1,2,4-oxadiazoles(8). It is worth mentioning that, in contrast to I, when V were boiled (6-8 hours) with hydrazine hydrate or with hydroxylamine no opening of the pyrimidine ring occured, the product isolated being the corresponding amidrazone (or amidoxyme) due to the nucleophile attack to the nitrile group.

The structures of the newly synthesised compounds were assigned on the basis of elemental microanalysis and spectral data. II, III and IV were obtained according to the following general procedure: The powdered I was stirred in aqueous ethanol with a triple molar excess of hydrazine (or hydroxylamine or arylhydrazine) for 5-10 min until a clear solution was formed. The reaction product was isolated after addition of 10% acetic acid, which caused crystallisation . When the reaction product was a liquid it was isolated by means of benzene extraction at pH 3 and further distillation under reduced pressure.

REFERENCES & NOTES

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3. C.Ainsworth, W.Buting, J.Davenport, M.Callender, M.McCowen, J.Med.Chem., 10(1967)208.
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5. XI melted at 103-104°C and was identical with 1,3,5-triphenyl-1,2,4-triazole described by H.Wolchove, Mh.Chem.,37(1916)476.
6. VIa,b and VIIIa,b were synthesised using a method published by us earlier: S.K.Robev, Dokl.Bolg.Akad.Nauk, 30(1977)719.
7. One mmole of VI was heated at 100°C for 5 min with 5 mmole of $PhNHNH_2$,the reaction mixture was cooled, treated with 10 ml of 5% acetic acid and stirred until solidification occurred. After drying the product was dissolved in benzene, one volume light petroleum was added and the filtered solution let to stay at -10°C. VII was isolated as yellowish crystals. VIIa - mp 158-160°C decomp; yield 70%; UV(dioxane) λ max(log e)nm 250(4,35); 319(4,49); IR(nujol) 3415, 3310, 3230, 3120(NH), 2190(CN), 1640(C=N)cm^{-1}. VIIb - mp 125-128°C decomp; yield 90%; UV(dioxane) λ max(log e)nm 254(4,40); 314(4,53); IR(nujol) 3385, 3322, 3240, 3140(NH), 2185(CN), 1635(C=N)cm^{-1}.
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