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CYCLOADDITIONS WITH ACYLHYDRAZONES. SELECTIVE DIASTEREOMERIC PYRAZOLIDINE SYNTHESIS AND NITRILE ACYLIMINE SYNTHONS

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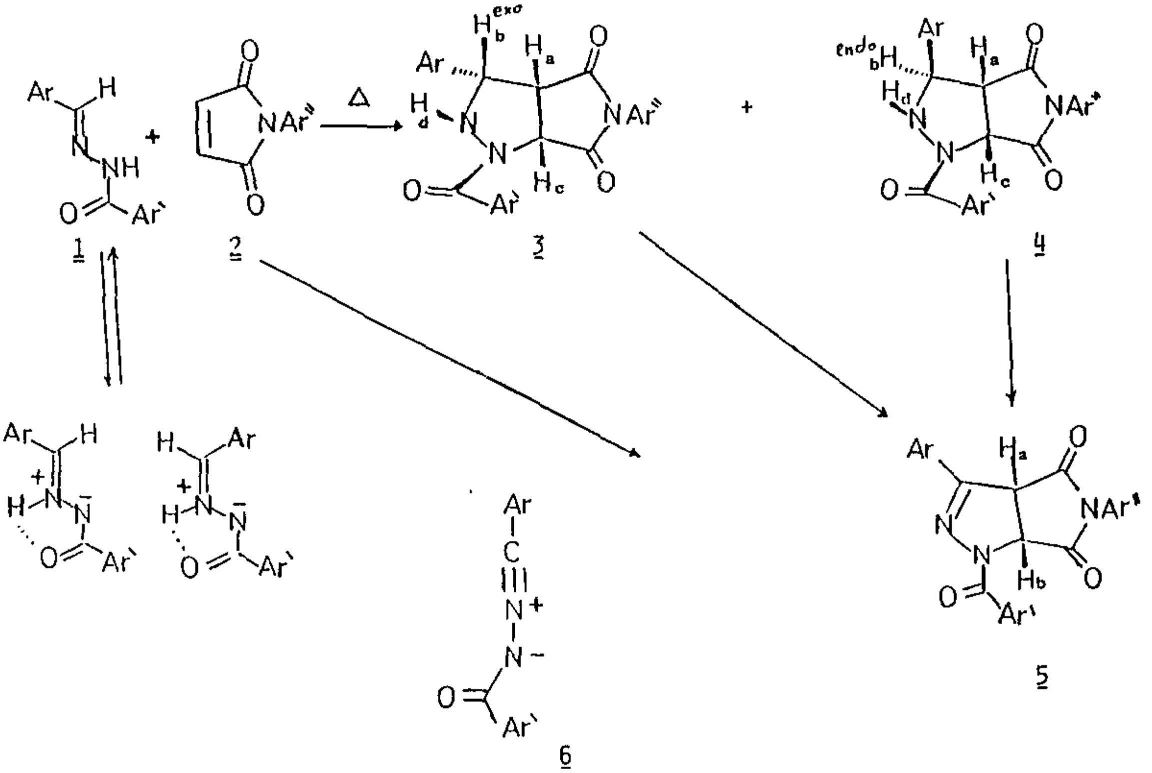
Abstract- Arylaldehydes N-acylhydrazones 1 undergo dipolar cycloadditions to N-arylmaleimides 2 to give two diastereomeric kinetic and thermodynamic pyrazolidines 3 and 4. Oxidation of 3 and 4 gave the corresponding pyrazolines 5 which were also obtained directly from compounds 1 and 2 in nitrobenzene. The present investigation offers an easy access to nitrile acylimine synthons 6.

A general principle for the synthesis of five-membered heterocycles has been introduced with the revolutionary development of the 1,3-dipolar cycloadditions[1].However the reaction depends on the availability of the precursors, especially those needed for the generation of the appropriate 1,3-dipolar species. Thus, although many nitrile imines have been successfully obtained from the appropriate precursors[1], their N-acyl derivatives have not, to the best of our knowledge, been reported. Recent reports showed that arylaldehyde N-phenylhydrazones undergo [3+2] cycloadditions to maleimides and acetylene dicarboxylates[2].

We have now investigated the reaction of arylaldehyde N-acylhydrazones 1 with N-arylmaleimides 2 as a representative dienophile.

When a mixture of 1a (1: Ar = Ar' = Ph, 0.1 mmol) and N-phenylmaleimide 2a (0.12 mmol) was heated at 170-180°C for 1.5 h, a 60% yield of crystalline compound 3a (3: Ar = Ar' = Ar'' = Ph) mp 249°C, could be isolated by first triturating the reaction mixture with chloroform and crystallising the remaining solid from acetic acid. Structure of 3a was assigned 3,3a-cis-3a,6a-cis-1-benzoyl-3,5-diphenylperhydropyrrolo[3,4-c]pyrazole-4,6-dione on the basis of elemental analysis and its spectral data. Ms (m/z) 397 (12%, M^+), 396 (45%). Ir (KBr): 3250 (NH), 1720 cm^{-1} (C=O). 60 MHz ^1H-nmr (DMSO-d_6): Signals for one H each at δ 4.05 (t, Ha), 4.62 (dd, Hb), 6.06 (d, Hc), and 6.8 (d, NH) ppm; Jab=5, Jac=5, Jbd=6Hz. On adding D_2O, the signal at δ =6.8 ppm disappeared and that at 4.62 changed to a doublet with Jab=5Hz.

When this reaction was carried out for 4 h, another stereoisomeric product 4a, mp 260°C, was obtained in 70% yield. Structure of 4a was assigned 3,3a-trans-3a,6a-cis-1-benzoyl-3,5-diphenylperhydropyrrolo[3,4-c]pyrazole-4,6-dione on the basis of its elemental analysis and its spectral data. Ms (m/z) 397 (41%, M^+). Ir (KBr) 3250 (NH), 1740 cm^{-1} (C=O). 90 MHz ^1H-nmr (DMSO-d_6): Signals for one H each at δ 4.22 (d, Ha), 4.90 (s, Hb), 5.95 (d, Hc), and 3.50 (s, NH) ppm; Jab=0, Jac=7Hz.



It is interesting to note that monitoring the reaction of 1a with 2a by ^{1}H-NMR spectroscopy showed the predominant formation of 3,3a-cis isomer 3a at an early stage of the cycloaddition. After the complete consumption of the both starting materials, 3a started to isomerize into the 3,3a-trans isomer 4a. The isomerization was completed in 4 h. Compound 3a was actually converted into 4a when heated at 170°C for 4 h, indicating that compound 3a is the kinetic product while 4a is the thermodynamic product. When compound 3a was heated with excess N-(p-chlorophenyl)maleimide at 170°C for 4 h compound 4b (4: Ar = Ar' = Ph, Ar" = p-ClC_6H_4) was isolated from the reaction mixture, and compound 4b was similarly converted into 4a by heating with excess 2a. This means that the isomerization of the kinetic 3a to thermodynamic product 4a proceeds through a reterocycloaddition route.

Adducts 3 and 4 have been selectively prepared in the controlled reactions of 1 with 2 in a variety of solvents such as xylene and bromobenzene. Table 1 lists some of the products 3 and 4 obtained from the appropriate 1 and 2.

Product*	mp	Ar	Ar'	Ar''	Ha	Hb	Hc	Hd(NH)	Jab	Jac	Jbd
3a(i)	249	C_6H_5	C_6H_5	C_6H_5	4.05(t)	4.60(dd)	6.06(d)	6.80(d)	5	5	6
3a(ii)					4.05(t)	4.60(d)	6.06(d)	—	5	5	—
3b(i)	250	C_6H_5	C_6H_5	C_6H_4Cl-p	4.02(t)	4.60(dd)	6.00(d)	6.70(d)	4	4	5.5
3b(ii)					4.02(t)	4.60(d)	6.00(d)	—	4	4	—
3c(i)	218	C_6H_5	$C_6H_4OCH_3$-p	C_6H_4Cl-p	4.00(t)	4.55(dd)	6.03(d)	6.70(d)	6	6	6
3c(ii)					4.00(t)	4.55(d)	6.03(d)	—	6	6	—
4a(i)	260	C_6H_5	C_6H_5	C_6H_5	4.20(d)	4.90(s)	5.95(d)	3.50(s)	0	7	0
4d(i)	255	C_6H_5	$C_6H_4OCH_3$-p	C_6H_5	4.00(d)	4.90(s)	5.97(d)	3.20(s)	0	8	0
4b(i)	236	C_6H_5	C_6H_5	C_6H_4Cl-p	4.00(d)	4.75(s)	5.80(d)	3.30(s)	0	7	0
4e(i)	258	C_6H_4Cl-m	C_6H_5	C_6H_5	4.10(d)	4.95(s)	6.00(d)	3.60(s)	0	7	0
4f(i)	231	$C_6H_4OCH_3$-p	$C_6H_4OCH_3$-p	C_6H_5	3.95(d)	4.90(s)	5.95(d)	3.70(s)	0	7	0
4c(i)	258	C_6H_5	$C_6H_4OCH_3$-p	C_6H_4Cl-p	4.08(d)	4.85(s)	5.93(d)	3.40(s)	0	8	0
5a(iii)	245	C_6H_5	C_6H_5	C_6H_5	5.10(d)	6.30(d)			10.5		
5b(iii)	250	C_6H_4Cl-m	C_6H_5	C_6H_5	5.00(d)	6.25(d)			10.5		

The ^1H-nmr was taken in (i) DMSO-d_6 ; (ii) DMSO-d_6 + D_2O and (iii) $CDCl_3$

*Satisfactory analysis for all new products 3 , 4, and 5 were obtained. Products 3 and 4 were obtained in 50-70% under the same conditions described for 3a and 4a. Products 5a,b were obtained in 90% from 3a, 4a and 4e by heating under reflux 0.5 h in ethanolic cupric chloride and in 30% by heating under reflux 5h in nitrobenzene. Compound 5a was also obtained in 85% by heating 4a in bromobenzene with equimolecular amount of bromine for 1 h. All products were crystallized from acetic acid.

The products 3 and 4 are readily oxidized to the corresponding pyrazoline derivatives 5 (Table 1) when heated in nitrobenzene or by the action of cupric chloride in ethanol or bromine in bromobenzene. Direct reaction of compounds 1 and 2 in nitrobenzene also leads to 5.

The present investigation gives an easy access to the otherwise unavailable N-acyliminonitrile synthons 6.

Interesting cycloaddition results with different dienophiles and other functionalized acylhydrazones, ethoxycarbonylhydrazones, thioacylhydrazones, semicarbazones, thiosemicarbazones and their derivatives were obtained and will be reported soon.

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