REGIOSELECTIVITY OF REACTIONS OF 2-FUROYL-N-ARYL NITRILE IMINE WITH SOME DIPOLAROPHILES

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Abstract. The regioselectivity of the cycloadditions of nitrile imines (1a-d), derived from 2-furoylhydrazidoyl chlorides (3a-d), to the C=C and C=S double bonds of the enol tautomer of acetylacetone and the resonance stabilized thiocyanate anion respectively was investigated. The results indicate that the reactions studied are dipole-LUMO controlled and that the larger orbital coefficient in the LUMO of 7 is on the carbon atom.

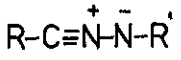
INTRODUCTION

Inspite of the copious literature[1-3] dealing with 1,3-dipolar cycloaddition reactions of different nitrile imines 1 derived from 1,3-elimination of HX from the corresponding hydrazidoyl halides 2, little attention, if any, has been given to reactions of 1 where R is a heterocyclic moiety. To help remedy this situation, the reactions of 3 with enol tautomer of acetylacetone and thiocyanate anion as dipolarophiles were investigated. Our objective was to shed some light on the effect of the heteroaryl substituent on the regioselectivity of the reactions of nitrile imines[4-7].

RESULTS AND DISCUSSION

The hydrazidoyl chlorides 3a-d were prepared by coupling 1-(2-furyl)-2-chloro-1,3-butanedione with diazotized anilines in sodium acetate buffered solution of ethanol (Scheme 1). The coupling products 3 are new and their structures followed their elemental analyses and spectral data (see experimental section). The structure of 3 was further substantiated by their chemical behaviour described below (Schemes 2 and 3).

Treatment of 3 with sodium acetylacetanoate in ethanol solution gave only 1-aryl-3-(2-furoyl)-4-acetyl-5-methylpyrazoles 4. TLC of the reaction mixture showed the absence of the other possible isomeric products 5



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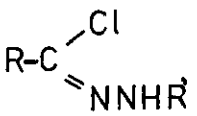

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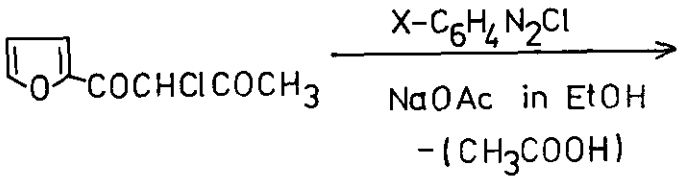

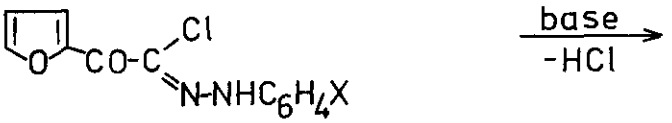

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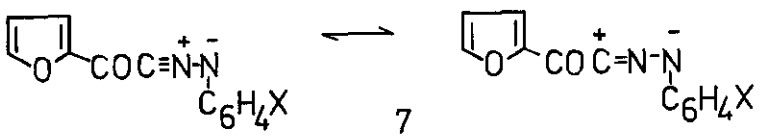

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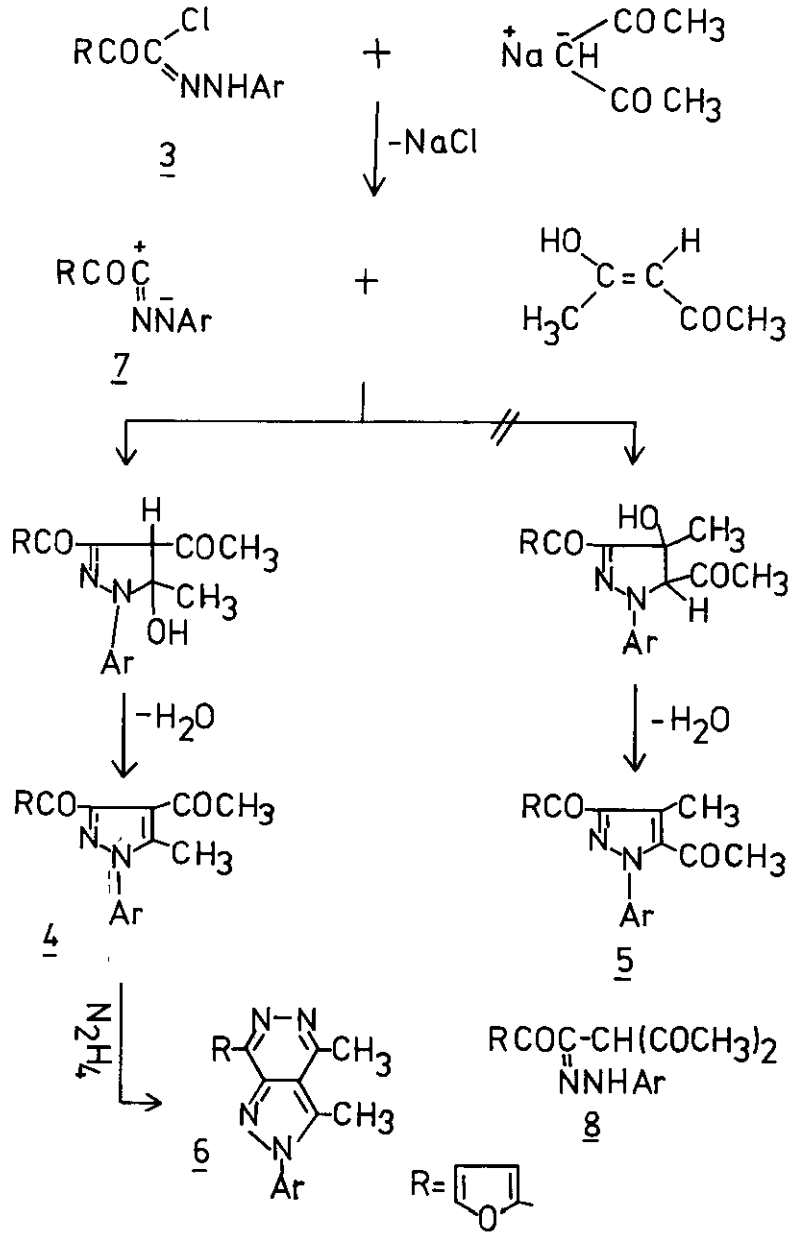
a) X = H c) X = p-Cl

b) X = p-CH_3 d) X = p-NO_2

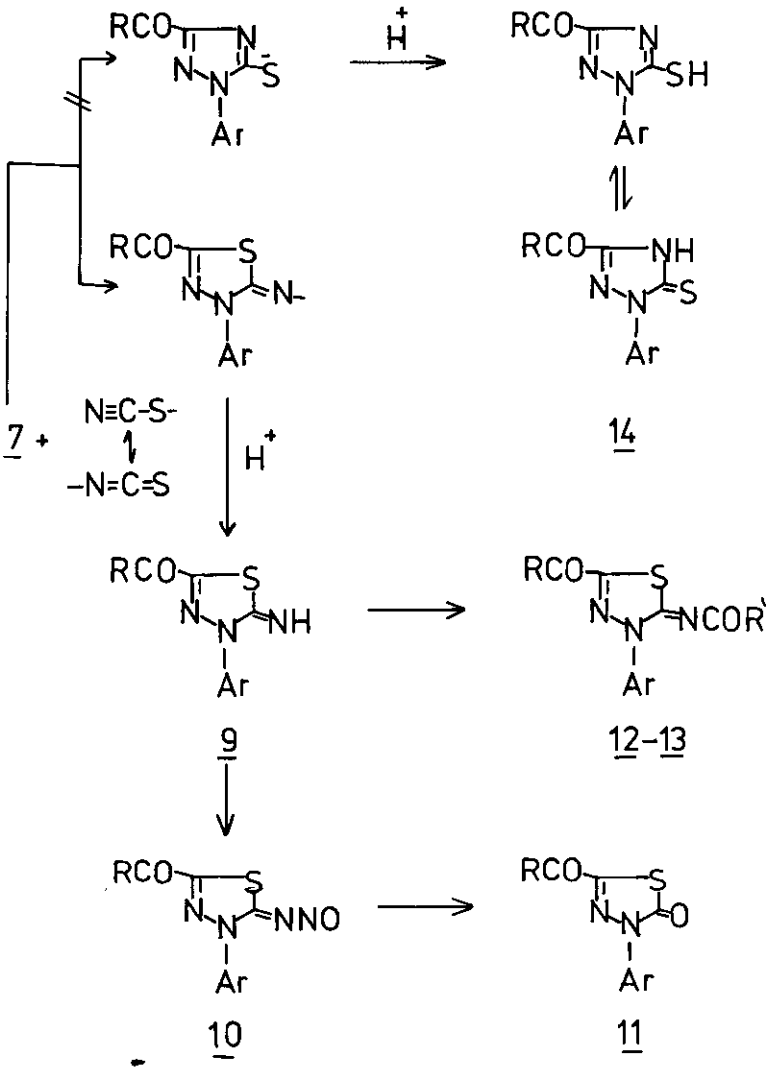
Scheme 1



Scheme 2

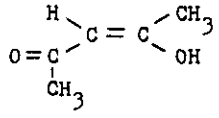
(Scheme 2). The structure of pyrazole 4 was established on the basis of analytical and spectroscopic data in addition to their chemical behaviour. For example, compounds 4 exhibit two characteristic singlets near δ 2.5 and 2.7 ppm assignable to the 5-CH_3 and 4-CH_3CO groups, respectively. Chemically, the products 4 gave no color with ethanolic ferric chloride solution and did not couple with diazotized aniline in the presence of sodium acetate or sodium hydroxide, thus excluding the open chain structure 8. The structure of 4 is further confirmed by their reaction with hydrazine hydrate. Thus, hydrazinolysis of 4 in refluxing ethanol gave 2H-pyrazolo-[3,4-d] - pyridazines 6 in almost qunatitative yield. The infrared spectra of the latter products showed no carbonyl bands. Also the location of the methyl group on a pyridazine carbon atom was evidence by the downfield shift (2.97 ppm) compared to the signal of the acetyl methyl group (2.70 ppm) at the C_4 in the corresponding 4-acetylpyrazoles. The formation of 6 from 4 and hydrazine hydrate provides an additional evidence for the exclusion of structure 5.

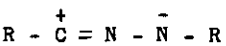
According to the frontier orbital treatment of 1,3-dipolar cycloadditions[5,6], the regioselectivity of addition will be determined primarily by the relative magnitude of the orbital coefficients in the HOMO and LUMO of the 1,3-dipole and dipolarophile involved in the reaction. The favoured cycloadduct will be that formed by union of the atoms with the largest coefficients. Calculations by CNDO/2 method made by Houk and coworkers[5,6] indicate that reactions of nitrile imine and monosubstituted electron rich alkenes are dipole-LUMO-dipolarophile-HOMO controllled. This is expected to be the case for polysubstituted alkenes as e.g. the enol tautomer of acetylacetone. This is because double and triple substitution with electron donating OH and CH_3 groups and/or conjugating CH_3CO group should further increase the energy gap between the dipole HOMO and dipolarophile LUMO. Furthermore, as it was shown that the larger orbital coefficient in the HOMO of monosubstituted ethylene is on the unsubstituted carbon, it would be expected that the HOMO of the enol tautomer of acetylacetone has the larger coefficient on C_1. This is because the effects of the CH_3, OH and CH_3CO groups would reinforce each other. Therefore the exclusive formation of 4 rather than 5 suggests that the LUMO of 7 has the larger coefficient on the carbon atom.



R=  ; R'=CH_3 , C_6H_5 ; Ar= XC_6H_4

Scheme 3





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The reaction of 3 with the thiocyanate anion in ethanol at room temperature gave 2-(2-furoyl)-4-aryl-5-imino-Δ^2-thiadiazolines 9, whose structures were deduced from their spectra and from their chemical reactions. described below (Scheme 3). IR spectra of 9 revealed no band in the 2000 - 2200 cm^{-1} region due to free SCN group. However, they showed bands at 3345 cm^{-1} (imino NH), 1645 (CO), and 1620 cm^{-1} (C= N). The electronic absorption pattern of 9 in the UV region was in each case characterized by maxima near λ 371 nm (log ε 3.0), 282 (logε 3.1) and 252 nm (logε 3.8) regions[4]. That the reaction of 3 with the thiocyanate anion leads to thiadiazoline derivatives 9 rather than the isomeric 5-mercapto-1,2,4-triazole 14 is substantiated further by chemical behaviour of the products obtained. Thus, nitrosation of 9 with sodium nitrite and acetic acid yields products identified as 2-furoyl-4-aryl-5-nitrosoimino-Δ^2-1,3,4-thiadiazoline 10. As typical N-nitroso derivatives, the nitrosation products 10 undergo elimination of nitrogen upon thermolysis in xylene and give the corresponding 1,3,4-thiadiazoline-5-one derivatives 11 (Scheme 3). In addition, treatment of 9 with benzoyl chloride in pyridine yields the corresponding N-benzoyl derivatives 12. Similarly with acetic anhydride, 9 gives the N-acetyl derivatives 13. These results (taken collectively), indicate that the cycloaddition reaction of 7 to thiocyanate anion occurs at the C = S rather than C = N bond.

This regioselectivity can also be rationalized in terms of the frontier orbital treatment. Since the thiocyanate anion is an electron rich dipolarophile, its reaction with 7 is expected to be controlled by the LUMO and HOMO of 7 and thiocyanate anion respectively. As the HOMO of the thiocyanate anion has the larger orbital coefficient on the sulfur atom[8,9], it is not unreasonable to conclude that the larger orbital coefficient in the LUMO of 7 is on the C-atom in agreement with the foregoing conclusion drawn from reaction of 7 with acetylacetone enol tautomer.

EXPERIMENTAL

Melting points were determined with an electrothermal melting point apparatus (Gallen Kamp) and are uncorrected. The IR spectra were measured on a

Pye-Unicam SP1000 spectrophotometer and UV spectra were run on Beckman DK2 spectrophotometer. PMR spectra were recorded on a Varian T60-A spectrometer. Elemental analyses were performed by Microanalytical Laboratory, Cairo University, Egypt.

Preparation of Hydrazidoyl Chlorides (3a-d) - A solution of α-chloro-1-(2-furyl)-1,3-butanedione (5 g, 0.025 mole) in ethanol (70 ml) was stirred for 5 min with sodium acetate (3 g) and chilled in an ice-salt bath to 0 - 5°C. To the resulting cold solution was added the desired diazonium salt (0.025 mole) solution. After the addition was completed, the reaction mixture was stirred for additional 1 hr. The crude solid obtained was collected , washed with water and recrystallized from ethanol. The hydrazidoyl chlorides 3a-d prepared are : compound 3a, m.p. 106°C, $C_{12}H_9O_2N_2Cl$, Anal. Found (calcd.): C, 57.58 (57.95); H, 3.4 (3.64); N, 11.30 (11.25); Cl, 14.13 (14.27)%; compound 3b, m.p. 118°C, $C_{13}H_{11}N_2O_2Cl$, Anal. found (calcd.): Cl, 13.40 (13.50)%; compound 3c , m.p. 210°C, $C_{12}H_8N_2O_2Cl_2$, Anal. found (Calcd): Cl, 25.00 (25.05)% and compound 3d, m.p. 257°C, $C_{12}H_8O_3N_4Cl$, Anal. found (calcd.): Cl, 11.98 (12.02)%.

Preparation of 1-Aryl-3-furoyl-4-acetyl-5-methylpyrazoles (4a-d) - To an ethanolic sodium ethoxide solution prepared by dissolving metallic sodium (0.11 g, 0.005 mole) in ethanol (20 ml) was added acetylacetone (0.5 g, 0.005 mole) with stirring. To the resulting solution, the appropriate hydrazidoyl chloride (0.005 mole) was added and stirring was continued for 30 min. The mixture was diluted with water. The solid precipitated was collected and recrystallized from ethanol to give the acetyl pyrazoles 4a-d. Compound 4a, m.p. 134°C, $C_{17}H_{14}N_2O_3$, Anal. Found (calcd.): C, 69.20 (69.34); H, 4.70 (4.79); N, 9.43(9.55)%; compound 4b, m.p. 84°C, $C_{18}H_{16}N_2O_3$, Anal. Found (calcd.): N, 9.14(9.12)%; compound 4c, m.p. 171°C, $C_{17}H_{13}ClN_2O_3$, Anal. Found (calcd.): N, 8.51 (8.55)%; and compound 4d, m.p. 225°C, $C_{17}H_{13}N_3O_5$, Anal. Found (calcd.): N, 12.32(12.43)%.

Hydrazinolysis of (4a-d) - A mixture of 4-acetyl-2-furoylpyrazole 4 (0.005 mole) and hydrazine hydrate (10 ml) was refluxed for 30 min and then cooled. Upon dilution with cold water the pyrazolopyridazine precipitated. The solid was collected, washed with water and recrystallized from ethanol. The pyrazolopyridazines prepared are : compound 6a, m.p. 265°C, $C_{17}H_{14}N_4O$, Anal. Found (calcd.): C, 70.12 (70.16); H, 4.75 (4.85); N, 19.27 (19.36)%; compound 6b, m.p. 260°C, $C_{18}H_{16}N_4O$, Anal. Found (calcd.): N, 18.42 (18.47)%; compound 6c,

m.p. 230°C, $C_{17}H_{13}ClN_4O_3$, Anal. Found (calcd.): N, 17.21 (17.31)% and compound 6d , m.p. 270°C, $C_{17}H_{13}N_5O_3$, Anal. Found (calcd.): N, 20.91 (20.96)% .

Preparation of 2-furoyl-4-aryl-5-imino-Δ^2-thiadiazolines (9a-d) - A solution of potassium thiocyanate (0.005 mole) in ethanol (5 ml) was added to a warm solution of hydrazidoyl chloride 4 (0.005 mole) in ethanol (20 ml). The reaction mixture was refluxed for 15 min, cooled and the crude product was collected. Recrystallization from ethanol gave the corresponding imino compounds 9a-d (Table 1).

Preparation of 2-furoyl-4-aryl-5-nitrosoimino-Δ^2-1,3,4-thiadiazolines (10a-d) - To a solution of 9 (0.5 g) in acetic acid (15 ml), a saturated solution of sodium nitrite was added dropwise while stirring in ice bath. The crude product separated was collected and recrystallized from ethanol to give the corresponding N-nitroso derivatives 10a-d (Table 1).

Preparation of 2-furoyl-4-aryl-Δ^2-1,3,4-thiadiazoline-5-ones (11a-d) - The appropriate N-nitroso compound 10 (0.5 g) was heated in dry xylene under reflux for 1 hr. The excess solvent was evaporated and the solid was recrystallized from methanol to give the products 11a-d (Table 1).

Preparation of 2-furoyl-4-aryl-5-N-benzoylimino-Δ^2-1,3,4-thiadiazolines (12a-d) - A mixture of compound 9 (0.2 g) and benzoyl chloride(0.5 g) was refluxed in pyridine (10 ml), cooled, poured on ice and acidified with dilute hydrochloric acid. The crude solid precipitated was collected and recrystallized from ethanol or acetic acid to give the products 12a-d (Table 1).

Preparation of 2-furoyl-4-aryl-5-N-acetylimino-Δ^2-1,3,4-thiadiazolines (13a-d)- Compound 9 (0.5 g) was refluxed in acetic anhydride (20 ml) for 15 min, cooled and poured on ice. The crude solid precipitated was collected and recrystallized from ethanol to give the products 13a-d (Table 1).

Table 1

Compound No.	M.p. °C	Molecular Formula	S % Found	S % Calcd.
	2-Furoyl-4-aryl-5-imino-Δ^2-1,3,4-thiadiazolines 9a-d			
9a	149	$C_{13}H_9N_3O_2S$	11.65	11.79
9b	163	$C_{14}H_{11}N_3O_2S$	11.27	11.21
9c	194	$C_{13}H_8ClN_3O_2S$	10.30	10.46
9d	255	$C_{13}H_8N_4O_4S$	10.00	10.11
	2-Furoyl-4-aryl-5-N-nitrosoimino-Δ^2-1,3,4-thiadiazolines 10a-d			
10a	135	$C_{13}H_8N_4O_3S$	10.55	10.64
10b	135	$C_{14}H_{10}N_4O_3S$	10.12	10.17
10c	151	$C_{13}H_7N_4O_3SCl$	9.54	9.56
10d	235	$C_{13}H_7N_5O_5S$	9.21	9.26
	2-Furoyl-4-aryl-Δ^2-1,3,4-thiadiazoline-5-ones 11a-d			
11a	146	$C_{13}H_8N_2O_3S$	11.67	11.75
11b	138	$C_{14}H_{10}N_2O_3S$	10.98	11.16
11c	274	$C_{13}H_7ClN_2O_3S$	9.97	10.46
11d	97	$C_{13}H_7N_3O_5S$	10.32	10.08
	2-Furoyl-4-aryl-5-N-benzoylimino-Δ^2-1,3,4-thiadiazolines 12a-d			
12a	255	$C_{20}H_{13}N_3O_3S$	8.40	8.52
12b	222	$C_{21}H_{15}N_3O_3S$	8.11	8.21
12c	243	$C_{20}H_{12}N_3O_3S\ Cl$	7.66	7.80
12d	228	$C_{20}H_{12}N_4O_5S$	7.53	7.61
	2-Furoyl-4-aryl-5-N-acetylimino-Δ^2-1,3,4-thiadiazolines 13a-d			
13a	191	$C_{15}H_{11}N_3O_3S$	10.25	10.20
13b	177	$C_{16}H_{13}N_3O_3S$	9.74	9.77
13c	201	$C_{15}H_{10}N_3O_3SCl$	9.21	9.19
13d	171	$C_{15}H_{10}N_4O_5S$	8.74	8.92

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