COMMUNICATIONS

DE LA FACULTÉ DES SCIENCES
DE L'UNIVERSITÉ D'ANKARA

Série B : Chimie

TOME : 29 ANNÉE : 1983

Regioselectivity Of The Reactions Of Aryl Carbamoyl -N- Aryl Nitrile Imines With Some Dipolarophiles.

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Faculté des Sciences de l'Université d'Ankara
Ankara, Turquie

Communications de la Faculté des Sciences de l'Universite d'Ankara

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Regioselectivity Of The Reactions Of Aryl Carbamoyl –N– Aryl Nitrile Imines With Some Dipolarophiles.

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(Received January 6, 1983; accepted March 7, 1983)

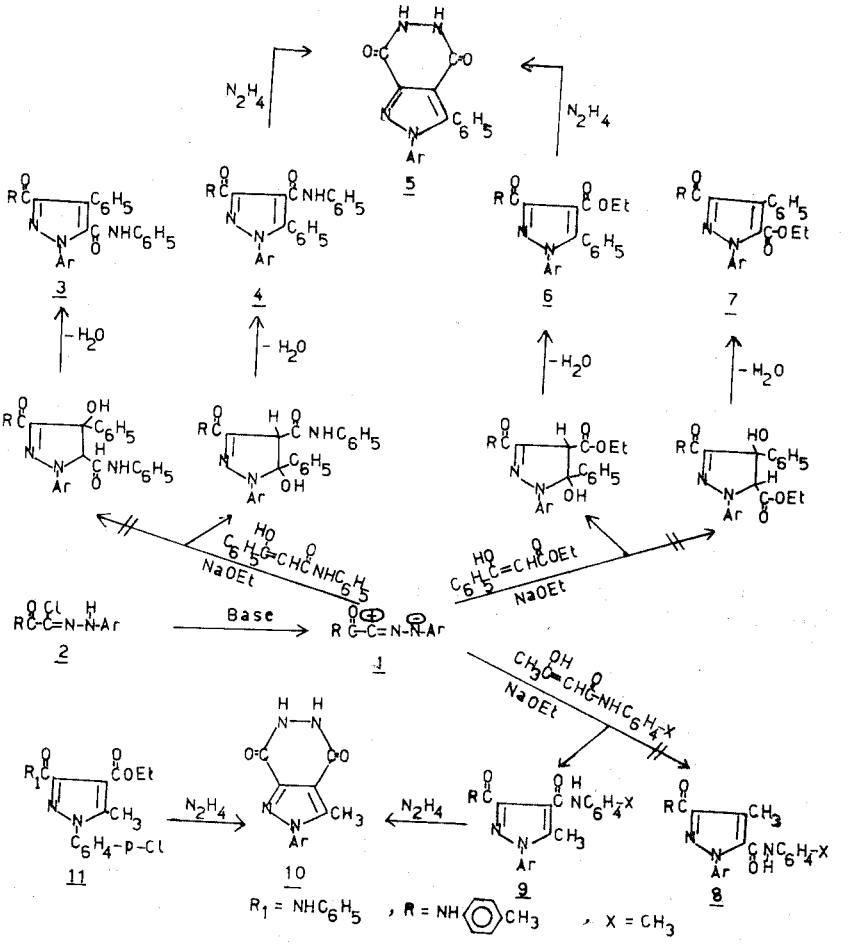
ABSTRACT

The regioselectivity of the cyloadditions of nitrile imines 1, derived from Aryl Carbamoyl hydrazidoyl chlorides 2, to the C=C and C=S double bonds of the enol tautomer of benzoyl acetanilide, ethyl benzoylacetate, p-acetoacetotoluidide 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 1 is on the carbon atom.

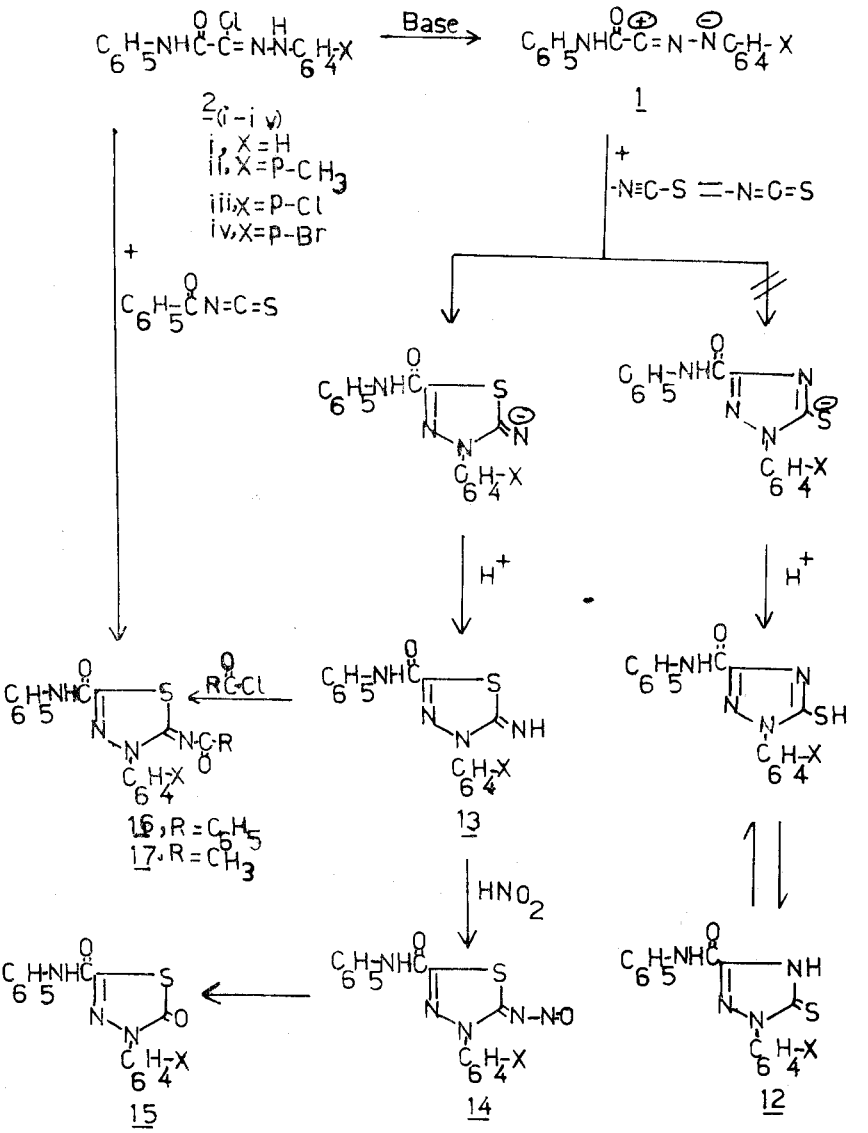
Inspite of the copious literature[1–4] dealing with 1,3 -dipolar cycloaddition reactions of different nitrile imines 1 derived from 1,3- elimination of HCl from the corresponding hydrazidoyl chlorides 2. The reactions of 2 with the enol tautomers of benzoylacetanilide, ethyl benzoylacetate, p-acetoacetotoluidide and thiocyanate anion as dipolarophiles were investigated. Treatment of 2 with sodium benzoylacetanilide in ethanol solution gave pyrazole derivates 4. TLC of the reaction product showed the absence of the other possible isomeric products 3. The structure of the pyrazole 4 was established on the basis of analytical and spectroscopic data in addition to their chemical behaviour. For example, compound 4_b reveald a singlet at δ 2.1 ppm assignable to methyl group (3H) of p-CH_3-C_6H_4-, multiplite from δ 7.1–7.9 ppm assignable to aromatic protons (19 H) and two singlets near δ 9.9 and 10.1 ppm assignable to NH protons of anilide (2H). Compound 4_c reacted with hydrazine hydrate to give the pyrazolo -[3, 4-d] -pyridazine derivatives 5. Compound 2 reacted also with ethyl benzoylacetate in sodium ethoxide to give the 4-ethoxycarbonyl pyrazole derivateives 6, which could be converted into 5 on treatment with hydrazine hydrate. The formation of 5 from the reaction of 6_a and hydrazine hydrate provides an additional evidence for the exclusion of structure 7. Thus, hydrazi-

nolysis of 4_c and 6_a to give the same product 5 is a further evidence for the suggested structures. On the other hand, compound 2 reacted with p-acetoacetotoluidide to give a product which could be formulated as 8 or tautomeric 9. Structure 9 was established for the reaction product based on analytical and spectral data. An uniquivocal support for the structure of 9 was acheived by the action of hydrazine hydrate on 9_a to give the pyrazolo- [3, 4-d] pyridazine derivative 10 which in turn, could be synthesised via the reaction of the pyrazole derivative 11[5] and hydrazine hydrate (cf. Scheme 1).

The reaction of 2 with the thiocyanate anion in ethanol gave 2-phenylcarbamoyl -4- aryl -5- imino -$\triangle^2$ -1, 3, 4- thiadiazolines 13. The structure of 13 was inferred from analytical and spectral data and from their chemical behaviour (cf. Scheme 2). IR spectra of 13 revealed no band in the 2000-2200 cm^{-1} region due to free SCN group. However, they showed bands at 3320 cm^{-1} (NH), 1665 cm^{-1} (C=O) and 1620 cm^{-1} (C=N). This indicated that the reaction of 2 with the thiocyanate anion leads to the formation of the thiadiazoline derivatives 13 rather than the isomeric 5-mercapto -1, 2, 4- triazole 12, Thus, nitrostion of 13, with sodium nitrite and acetic acid, yields products identified as 2- phenyl carbamoyl -4- aryl -5- N- nitrosoimino -$\triangle^2$- 1. 3, 4- thiadiazolines 14. As typical N-nitroso derivatives, the nitrosoation products 14 undergo elimination of nitrogen upon thermolysis in nitrobenzene to give the corresponding $\triangle^2$ -1, 3, 4- thiadiazoline -5- one derivatives 15. In addition, treatment of 13 with benzoyl chloride in pyridine yields the corresponding N-benzoyl derivatives 16. The same products 16 could be obtained by the reaction of 2 with benzoylisothiocyanate in dry acetone. The formation of 16 by the latter method gives a conclusive evidence for their structure of 13. Similarly, compounds 13 reacted with acetic -acetic anhydride mixture to give the N-acetyl-derivatives 17. These results (taken collectively), indicate that the cycloaddition reaction of 1 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 of 1,3-dipolar cycloadditions.[6,7] Since the thiocyanate anion is an electron rich dipolarophile, its reaction with 1 is expected to be controlled by the LUMO and HOMO of 1 and thiocyanate anion respectively. As the HOMO of the thiocyanate anion has the larger orbital coefficient on the sulphur atom[8,9].



Scheme I


Base
1
2 (i - iv)
i, X = H
ii, X = p-CH3
iii, X = p-Cl
iv, X = p-Br
+
-N≡C-S ⇌ -N=C=S
H+
H+
RCOCl
16, R = C6H5
17, R = CH3
HNO2
13
14
15
12

Scheme II

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded in KBr on a Pye Unicam SP-1100 spectrophotometer. ^{1}HNMR were recorded on a Varian A-60 spectrometer and chemical shifts are expressed in δ units ppm down field from TMS as the internal standard. Analytical data were obtained from the Micro-analytical data unit at Cairo University.

General method to prepare pyrazole derivatives 4,6,9:

To an ethanolic sodium ethoxide solution prepared by dissolving metallic sodium (0.11 g, 0.005 mole) in ethanol (20 ml) was added benzoylacetanilide or ethyl benzoylacetate or p-acetoacetotoluidide (0.005 mole) with stirring. To the resulting solution, the hydrazidoyl chloride 2 (0.005 mole) was added and strring was continued for 1 hr. The reaction was left overnight at room temperature. The solid precipitated was collected and recrystallized from suitable solvent to give pyrazole derivatives 4,6,9 respectively. (cf. table 1).

Pyrazolo -[3, 4-d]- *pyridazine derivatives* 5, 10:

A mixture of pyrazoles 4c or 6a and (9a or 11[5]) was refluxed for 2 hrs with hydrazine hydrate, then the reaction mixture was poured into ice-water, the solid precipitated was collected and recrystallized from ethanol to give pyrazolo -[3, 4-d] pyridazine derivatives 5, 10 respectively:- Compound 5 formed white powder m.p. $> 265^0$ c, yield 55 %. calcd. for $C_{17}H_{11}N_4O_2Cl$ (338.5) C; 60.26; H, 3.2; N, 16.54; Cl, 10.4 % found; C, 59.9; H, 3.1; N, 16.6.; Cl, 10.2 %.

Compound 10 formed white powder mp. $> 265^0$c. yield 63 %. calcd. for $C_{12}H_9N_4O_2Cl$ (276.5) C; 52.07; H, 3.25; N, 20.25; Cl, 12.8 % found; C, 51.9; H, 3.2; N, 20.4; Cl, 12.7 %.

Preparation of 2- *Phenylcarbamoyl* -4- *aryl* -5- *imino* -$\triangle^2$- 1, 3, 4- *thiadiazolines* 13 i-iv:

A solution of potassium thiocyanate (0.012 mole) in ethanol (25 ml) was added to hydrazidoyl chloride 2 (0.01). The reaction mixture was refluxed for 2 hrs, then poured into cold water, the solid product was collected and rectystallized from ethanol to imino compounds 13 i-iv (Table 2).

Preparation of 2-*Phenylcarbamoyl* -4- *aryl* -5- N- *nitrosoimino* $\triangle^2$ -1, 3, 4- *thiadiazolines* 14 *i-iv*:

To a solution of 13 i-iv (0.8 g) in acetic acid (20 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 14 i-iv (Table 2).

Preparation of 2- *Phenylcarbamoyl* -4- *aryl* -$\triangle^2$- 1, 3, 4- *thiadiazoline* -5- *one* 15 *i-iv*:

The appropriate N- nitroso compound 14 i-iv (1 g) was refluxed 3 hrs in dry nitrobenzene. The excess solvent was evaporated and the solid was collected and washed by pet. ether (60/80) and recrystallized from ethanol to give thiadiazoline 5-one derivatives 15 i-iv (Table 2).

Preparation of 2- *Phenylcarbamoyl* -4- *arly* -5- *N- benzoylimino-* $\triangle^2$ -1, 3, 4- *thiadiazolines* 16 *i-iv*:

Method A

A mixture of compound 13 i-iv (0.01 mole) and benzoyl chloride (0.01 mole) was refluxed 90 minutes in pyridine (20 ml), cooled, then poured into ice and acidified with hydrochloric acid. The crude solid precipitated was collected and recrystallized from acetic acid to give N-benzoyl derivatives 16 i-iv

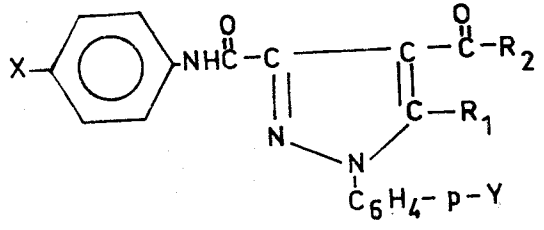
Method B

To a solution of benzoylisothiocyanate (prepared from NH_4SCN (0.12 mole) and benzoyl chloride (0.1 mole) was refluxed in dry acetone for 5 minutes) hydrazidoyl chloride 2 was added, the reaction mixture was refluxed additional 2 hrs, then poured into ice-water, the solid product was collected and recrystallized from acetic acid to give 16 i-iv (m.p. and mixed m.p. are the same in two cases) (Table 2).

Preparation of 2-*Phenylcarbamoyl* -4- *aryl* -5- *acetylimino* -$\triangle^2$- 1, 3, 4 *thiadiazolines* 17 i-iv:

Compound 13 i-iv (0.5 g) was refluxed in acetic anhydride/acetic acid (20 ml) for 30 minutes, cooled and poured on ice. The crude solid precipitate was collected and recrystallized from ethanol to give the N-acetyl derivatives 17 i-iv (Table 2).

TABLE 1



List of new pyrazoles derivates. $4_{a-c}, 6_{a,b}, 9_{a-c}$

Compound No.	R_1	R_1	X	Y Solvent of crystal	m.p.	Molecular formula formula	Elemental analysis Calcd/Found % C	H	N
4_a	C_6H_5	NHC_6H_5	H	H acetic acid	193 C°	$C_{26}H_{22}N_4O_2$	75.9	4.8	12.2
							75.6	4.6	12.1
4_b	C_6H_5	NHC_6H_5	CH_3	H acetic acid	188 C°	$C_{30}H_{24}N_4O_2$	76.2	5.1	11.8
							76.1	4.9	11.5
4_c	C_6H_5	NHC_6H_5	CH_3	Cl acetic acid	214 C°	$C_{30}H_{23}N_4O_2$ Cl.	71.1	4.5	11.1
							70.8	4.4	10.9
6_a	C_6H_5	OC_6H_5	CH_3	Cl ethyl alc.	210 C°	$C_{26}H_{22}N_3O_3$ Cl.	67.8	4.6	9.2
							67·8	4.6	9.2
6_b	C_6H_5	OC_6H_5	CH_3	NO_2 ethyl alc.	236 C°	$C_{26}H_{22}N_4O_5$	66.3	4.7	11.9
							66.0	4.5	11.8
9_a	CH_3	NHC_6H_4p-CH_3	CH_3	Cl acetic acid	248 C°	$C_{26}H_{23}N_4O_2$ Cl.	68.0	5.0	12.2
							67.8	4.9	12.1
9_b	CH_3	NHC_6H_4-p-CH_3	CH_3	NO_2 acetic acid	268 C°	$C_{26}H_{23}N_5O_4$	66.5	4.9	14.9
							66.3	4.9	14.7
9_c	CH_3	NHC_6H_4-p-CH_3	CH_3	CH_3 acetic acid	206 C°	$C_{27}H_{26}N_4O_2$	73.9	5.9	12.8
							73.9	5.7	12.7

IR of all prepared compounds were made and are in good agrement with structure proposed.

TABLE 2.

Lis of new Δ^2– 1,3,4- thiadiazolines derivatives.

Compound No.		M.p.	Cry. solvent	Yield%	Mol. Formula	Calcd. C. (Found) H Analysis %.		S
13	i	113 C°	ethanol	93	$C_{15}H_{12}N_4OS$	60.1 (60.0)	4.1 (3.9)	10.8 (10.9)
	ii	185 C°	ethanol	89	$C_{16}H_{14}N_4OS$	61.9 (61.7)	4.5 (4.4)	10.3 (10.2)
	iii	165 C°	ethanol	90	$C_{15}H_{11}N_4OS$ cl	54.5 (54.4)	3.3 (3.1)	9.7 (9.8)
	iv	178 C°	ethanol	94	$C_{15}H_{11}N_4OS$ Br	48.0 (47.8)	2.9 (2.8)	8.5 (8.3)
14	i	139 C°	ethanol	76	$C_{15}H_{11}N_5O_2S$	55.4 (55.3)	3.4 (3.3)	9.8 (9.6)
	ii	145 C°	ethanol	75	$C_{16}H_{13}N_5O_2S$	56.6 (56.3)	3.8 (3.6)	9.4 (9.2)
	iii	137 C°	ethanol	79	$C_{15}H_{10}N_5O_2Scl$	50.1 (50.0)	2.8 (2.9)	8.9 (8.7)
	iv	148 C°	ethanol	81	$C_{15}H_{10}N_5O_2SBr$	44.5 (44.2)	2.5 (2.3)	7.9 (7.6)
15	i	107 C°	ethanol	64	$C_{15}H_{11}N_3O_2S$	60.6 (60.5)	3.7 (3.4)	10.8 (10.5)
	ii	151 C°	ethanol	60	$C_{16}H_{13}N_3O_2S$	61.7 (61.4)	4.2 (4.1)	10.3 (10.1)
	iii	130 C°	ethanol	66	$C_{15}H_{10}N_3O_2Scl$	54.3 (54.1)	3.0 (3.8)	9.6 (9.5)
	iv	121 C°	ethanol	71	$C_{15}H_{10}N_3O_2S$ Br	47.9 (47.8)	2.6 (2.3)	8.5 (8.4)
16	i	229 C°	CH_3COOH	88	$C_{22}H_{16}N_4O_2S$	66.0 (65.8)	4.0 (3.9)	8.0 (7.8)
	ii	198 C°	CH_3COOH	79	$C_{23}H_{18}N_4O_2S$	66.7 (66.4)	4.3 (4.1)	7.7 (7.5)
	iii	232 C°	CH_3COOH	84	$C_{22}H_{15}N_4O_2Scl$	60.7 (60.6)	3.4 (3.2)	7.4 (7.1)
	iv	221 C°	CH_3COOH	90	$C_{22}H_{15}N_4O_2S$ Br	55.1 (55.2)	3.1 (2.9)	6.7 (6.7)
17	i	205 C°	ethanol	81	$C_{17}H_{14}N_4O_2S$	60.4 (60.2)	4.1 (3.8)	9.5 (9.2)
	ii	217 C°	ethanol	74	$C_{18}H_{16}N_4O_2S$	61.4 (61.3)	4.5 (3.4)	9.1 (8.8)
	iii	179 C°	ethanol	76	$C_{17}H_{13}N_4O_2Scl$	54.7 (64.5)	3.5 (3.3)	8.6 (8.3)
	iv	195 C°	ethanol	79	$C_{17}H_{13}N_4O_2SBr$	48.9 (48./)	3.1 (2.9)	7.7 (7.8)

IR of these compounds were made and are in good agreement with structures proposed.

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