Synthesis of 7-Aryl-2-cinnamyl-8-toxycarbonyl[1,2,4]Triazolo [1,5-a]pyridine via 2-etoxycarbonylcinnamonitriles with 2^{-}-cinnamoyl-2-cyanoacetohydrazide

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Abstract:

A series of 7-aryl-2-cinnamyl-8-etoxycarbonyl[1,2,4]triazolo[1,5-a]pyridine have been prepared by the reaction of 2-etoxycarbonylcinnamonitriles with 2^{-}-cinnamoyl-2-cyanoacetohydrazide. An alternative cyclization leading to the formation of piperidinium pyrazolo[3,4-b]pyridinides. This compounds were isolated from the reaction mixture as the corresponding piperidinium salts due to the high stability of the heterocyclic anion. Acidification with dilute hy- drochloric acid yielded the neutral 7-aryl-2-cinnamyl-8-etoxycarbonyl[1,2,4] triazolo[1,5-a]pyridine. Depending on the reaction conditions.

الخلاصة

تم تحضير مجموعة جديدة من 7–اريل–2–سينامايل–8–أيتوكسي كاربونيل[1,2,4]ترايزول[1,5-a] بردين.من خلال تفاعل 2–ايتوكسي كاربونيل سينامونتريل مع 2'–سينامويل–2–سيانو اسيتوهايدرازد. هذا التفاعل . يقود الى خيار أخر لتكوين مركبات حلقية جديدة هي ببريدينيوم بريزول [3,4-b]بردنيداس. هذه المركبات حلقية جديدة. يمكن فصل هذه المركبات على شكل ملح نتيجة الى أستقرار الأنيون (أيون سالب الشحنة) للمركبات الحلقية. ومن خلال معاملة الراشح مع محلول حامض الهيدروكلوريك يتكون راسب أبيض وعند تشخيص هذا الراسب تبين أنه المركب 7–اريل–2–سينامايل–8–أيتوكسي كاربونيل[1,2,4]ترايزول[1,5-a] بردين.

Introduction

The methods described for the synthesis of [1,2,4]triazolo[1,5-a]pyridine include: (a) reaction of 1,2-diaminopyridine derivatives with compounds such as carboxylic acids and esters [Irikura and Suzne, 1980], 1,3-diketones [Kubo, *et al.*,1979] and acetylene derivatives [Gewald, *et al.*, 1975]. (b) Cyclization of *N*-substituted aminopyridines [Davis and Jones ,1975]. (c) A copper catalyzed reaction of pyridine derivatives [Ueda and Nagasawa, 2009]. (d) More of these compounds have been prepared by cycloaddition reaction between *N*-aminomethyl-pyridinium and substituted benzonitriles in the presence of KOH at room temperature [Guolin Zhang and Yongzhou, 2007]. (e) These compounds have been prepared in good yield from aminopyridines [Reichelt, *et al.*, 2010]. Most of these consist in intermolecular multistep processes. (f) The compounds via reaction of arylidenemalononitriles with 2-[(substituted amino) thiocarbonyl] acetohydrazides, in refluxing ethanol in the presence of triethylamine [Girgis and Barsoum ,2009].

Our group have previously performed a very convenient, one step method for synthesis of [1,2,4]triazolo[1,5-a]pyridines **1** from the reaction of 2^{-}-benzoyl-2-cyanoaceto-hydrazide 2^{-}-acetyl-2-cyanoacetohydrazide, and 2-cyano-2^{-}-phenylacetylacetohydrazide **2** [Ali *et al.*,1992; Ali *et al.*,1993a, Ali *et al.*,1993b] with 2-cyanocinnamonitriles **3** [Corson and Stoughton, 1941]. Interestingly, substituting the etoxycarbonyl group for the cyano group in cinnamonitriles **3** led to a competitive cyclization to pyrazolo[3,4-b] pyridinones **4** which were also obtained, in one step as the piperidinium salt [Ali *et al.*,1992].

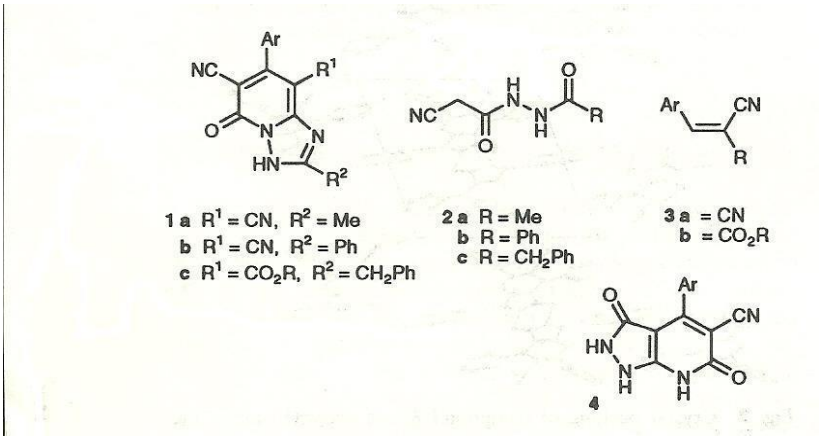
In this paper we report the reaction of 2-etoxycarbonylcinnamonitriles **6** with 2^{-}-cinna-
moyl-2-cyanoacetohydrazide **5** leads to the formation of 7-aryl-2-cinnamyl-8-etoxycarbo-nyl[1,2,4]triazolo[1,5-a]pyridine **12**. Now, an alternative cyclization can take place and,

in addition to the [1,2,4]triazolo[1,5-a]pyridines **12**, the novel pyrazolo[3,4-b]pyridinones **10** are obtained as the corresponding piperidinium salts (Scheme II).

The preparative of [1,2,4]triazolo[1,5-a]pyridines **1** which have proved their usefulness in many applications such as:

(a) Pharmaceuticals, complexing agent, or fluorescent brighteners [Callejo, *et al,*1990)].
(b) Anti-inflmmatory activity agents and anti-neoplastic agents [Girgis and Barsoum, 2009].
(c) Anti-tumor activities [Guolin Zhang and Yongzhou, 2007].
(d) Anti-bacterial agents [Magda *et al.*, 2004].
(e) Novel [1,2,4]triazolo[1,5-a]pyridine derivatives used in the treatment of various neurological and physiological disorders [American patent 12/777776, 2010].

The data of IR, ^{1}H-nmr, C.H.N analysis of pyrazolo[3,4-b]pyridinones **10** are not written in this paper, because they have been resulted through the reaction of 2-metoxycarbonylcinnamonitriles with 2$^-$-cinnamoyl-2-cyanoacetohydrazide and, this paper under the publish.



Experimental

Melting point were determined in capillary tubes in a Electrothermal 9200 apparatus and are uncorrected. ^{1}H-nmr spectra were recorded at 300 MHz on a Varian VXR 300s spectrometer. All nmr spectra were recorded as dimethyl sulfoxide solutions, chemical shifts being given as δ values with respect to tetramethylsilane as the internal standard. The ir spectra were measured with a Perkin-Elmer 781 instrument as potassium bromide pellets. All instruments which are exist in the University of Complutense-College of organic chemistry. Microanalyses were performed by the Universidad Complutense Microanalytical Service. The reactions were monitored by tlc performed on silica gel plates (Merck 60-F) and using chloroform-methanol or toluene-ethyl acetate as eluant.

Cyanoacetohydrazide, malononitrile, and piperidine were obtained from commercial sources (Aldrich and Merck) and were used without further purification. Aromatic aldehydes were distilled before use. Benzylidenemalononitrile was also a commercial product, but the remaining arylidenemalononitriles were prepared from aromatic aldehydes and malononitrile following the standard procedure [Ali *et al.*,1993b].

2′-Cinnamoyl-2-cyanoacetohydrazide 5 .

To a stirred solution of 2-cyanoacetohydrazide **1a** (1.98g, 18.8 mmoles) in 5 ml of water at 0 ^{0}C, 3-phenylpropenoyl chloride (30 mmoles) from a dropping funnel and a solution of potassium carbonate (1.29g) in 1.5 ml of water were added. After 20 minutes a precipitate was formed. The solid was collected by filtration and recrystallized from ethanol to yield white crystals (65% yield), mp 216-218^0; ir: 3200 (NH), 2260 (CN), 1680 (C=O), 1640 (C=O), cm^{-1}; ^{1}H-nmr: δ 3.78 (2H, s, CH_2), 6.65 (1H, d, CH=, J= 16.2 Hz), 7.38 (3H, m, ArH), 7.53 (1H, d, =CH, J= 16.2 Hz) 7.58 (2H, m, ArH), 10.35 (1H, bs, NH), and 10.48 (1H, bs, NH).

Anal. Calcd. for $C_{12}H_{11}N_3O_2$: C%, 62.90; H%, 4.80; N%, 18.35

Found: C%, 62.70; H%, 4.75; N%, 18.45

7-Aryl-2-cinnamyl-6-cyano-8-etoxycarbonyl-5-oxo[1,2,4]triazolo[1,5-a] pyridine 12 and Piperidinium 4-Aryl-1-cinnamoyl-5-cyano-3,6-dioxopyrazolo[3,4-] pyridinides 10. General procedure:

To a suspention of equimolares 2′-Cinnamoyl-2-cyanoacetohydrazide **5** (0.46 gm., 2mmol) and the corresponding arylidenecyanoacetate **6a-e** (2 mmol) in dry ethanol or absolute merhanol, equimolar of piperidine (2 mmol) were added. The reaction mixture was refluxed with stirring for available length of time (7-27) until the stsrting material was disappear and a solid has been precipitate in the reaction mixture. The ppt. was collected by filtration and recrystalzed from appropriate solvent. This compound was found to be corresponding piperidinium 4-aryl-1-cinnamoyl-5-cyano-3,6-dioxopyrazolo[3,4-b] pyridinides **10**. To the mothers liquors was added 10% hydrochloric acid (10-15 cm^3), and the mixture was stirred for 30 min., then left at room temperature. A white solid was corresponding to the 7-aryl-2-cinnamyl-6-cyano-8-etoxycarbonyl-5-oxo-[1,2,4]triazolo[1,5-a]pyridine **12** precipitated out. It was collected by filtration and washed with plenty of water (neutral PH).

2-Cinnamyl-6-cyano-8-etoxycarbonyl-5-oxo-7-phenyl[1,2,4]triazolo[1,5-a] pyridine 12a.

This compound was obtained in 41% yield, m.p. 340-342 ^{0}C (acetonitrile); ir: 3300-3100 (NH), 2220 (CN), 1700 (COO), 1650 (CO) cm^{-1}; ^{1}H-nmr: 0.65 (3H,t, CH_3), 3.85 (2H, d, CH_2O), 5.01 (1H, s , NH), 7.20-8.00 (12H, m, ArH, CH=CH).

Anal. Cald. For $C_{24}H_{18}N_4O_3$: C%, 70.25; H%, 4.40; N%, 13.65

Found: C%, 69.95; H%, 4.50; N%, 13.60

2-Cinnamyl-6-cyano-8-etoxycarbonyl-7-[*p*-methylphenyl]-5-oxo[1,2,4] triazolo[1,5-a]pyridine 12b.

This compound was obtained in 45% yield, m.p. >330 ^{0}C (acetonitrile); ir: 3300-3100 (NH), 2220 (CN), 1700 (COO), 1650 (CO) cm^{-1}; ^{1}H-nmr: 0.74 (3H,t, CH_3), 2.38 (3H, s, CH_3) 3.91 (2H, q, CH_2O), 5.01 (1H, s , NH), 7.10-7.55 (8H, m, ArH, CH=), 7.72 (2H, m, ArH), 8.00 (1H, d, =CH)

Anal. Cald. For $C_{25}H_{20}N_4O_3$: C%, 70.75; H%, 4.70; N%, 13.20

Found: C%, 70.80; H%, 4.85; N%, 13.20

Piperidinium1-Cinnamoyl-5-cyano-4-[*p*-methylphenyl]-3,6-dioxopyrazolo [3,4-b] pyridinides 10b.

According to the general procedure, the reaction mixture was finished after 12 hours, with 26% yield .

2-Cinnamyl-6-cyano-8-etoxycarbonyl-7-[*p*-methoxyphenyl]-5-oxo[1,2,4] triazolo [1,5-a]pyridine 12c.

This compound was obtained in 49% yield, m.p. 300-302 ^{0}C (acetonitrile); ir: 3300-3100 (NH), 2220 (CN), 1700 (COO), 1650 (CO) cm^{-1}; ^{1}H-nmr: 0.78 (3H,t, CH_3), 3.81 (3H, s, CH_3O) 3.93 (2H, q, CH_2O), 5.01 (1H, s , NH), 7.02 (2H, d, ArH, J= 8.4 Hz), 7.24 (2H, d, ArH, J= 8.4 Hz), 7.32 (1H, d, CH=, j= 16.2 Hz), 7.46 (3H, m, ArH), 7.73 (2H, d, ArH), 8.00 (1H, d, =CH, J= 16.2 Hz).

Anal. Cald. For $C_{25}H_{20}N_4O_4$: C%, 68.20; H%, 4.55; N%, 12.75
Found: C%, 67.95; H%, 4.70; N%, 12.95

Piperidinium 1-Cinnamoyl-5-cyano-4-[*p*-methoxyphenyl]-3,6-dioxopyra-zolo[3,4-b] pyridinides 10c.

According to the general procedure, the reaction mixture was finished after 8 hours, with 26% yield.

7-[*p*-chlorophenyl]-2-Cinnamyl-6-cyano-8-etoxycarbonyl-5-oxo[1,2,4] triazolo [1,5-a] pyridine 12d.

This compound was obtained in 35% yield, m.p. 375-377 ^{0}C (acetonitrile); ir: 3300-3000 (NH), 2220 (CN), 1700 (COO), 1650 (CO) cm^{-1}; ^{1}H-nmr: 0.79 (3H,t, CH_3), 3.95 (2H, q, CH_2O), 5.01 (1H, s , NH), 7.30-7.60 (8H, m, ArH, CH=), 7.72 (2H, d, ArH), 7.95 (1H, d, =CH)

Anal. Cald. For $C_{24}H_{17}ClN_4O_3$: C%, 64.80; H%, 3.80; N%, 12.60
Found: C%, 64.70; H%, 3.95; N%, 12.50

Piperidinium 4-[*p*-chlorophenyl]-1-Cinnamoyl-5-cyano-3,6-dioxopyra-zolo [3,4-b] pyridinides 10d.

According to the general procedure, the reaction mixture was finished after 11 hours, with 17% yield.

Piperidinium 5-Cyano-3,6-dioxo-4-phenylpyrazolo[3,4-b]pyridinides 13a.

According to the general procedure, the reaction mixture was finished after 27 hours, with 24% yield [Ali *e al.*,1993a] (See scheme III).

Piperidinium 2-cinnamyl-6-cyano-8-etoxycarbonyl-7-[*p*-nitrophenyl]-5-oxo [1,2,4] triazolo[1,5-a]pyridinide 11e.

This compound was obtained in 63% yield, m.p. 264-265 ^{0}C (ethanol); ir: 3000-2300 (br, b), 2200 (CN), 1700 (COO), 1650 (CO) cm^{-1}; ^{1}H-nmr: 0.76 (3H,t, CH_3), 1.51 (2H, m, CH_2 piperidinium), 1.59 (4H, m, $2CH_2$ pip.), 2.98 (4H, m, $2CH_2$ pip.), 3.3 (2H, q, CH_2O), 7.20-7.40 (4H, m, ArH, CH=), 7.55 (2H, d, ArH), 7.60-7.80 (3H, m, =CH, ArH), 8.26 (4H, m, ArH, NH_2).

Anal. Cald. For $C_{29}H_{28}N_6O_5$: C%, 64.45; H%, 5.20; N%, 15.55
Found: C%, 64.15; H%, 5.05; N%, 15.75

2-cinnamyl-6-cyano-8-etoxycarbonyl-7-[*p*-nitrophenyl]-5-oxo [1,2,4] triazolo [1,5-a] pyridine 12e.

This compound was obtained in 14% yield, m.p. >380 ^{0}C (acetonitrile or DMSO); ir: 3300-3000 (NH), 2220 (CN), 1700 (COO), 1650 (CO) cm^{-1}; ^{1}H-nmr: 0.70 (3H,t, CH_3), 3.90 (2H, q, CH_2O), 5.0 (1H, s , NH), 7.30-8.00 (9H, m, ArH, CH=CH), 8.35 (2H, m, ArH).

Anal. Cald. For $C_{24}H_{17}N_6O_5$: C%, 63.30; H%, 3.75; N%, 15.40
Found: C%, 63.45; H%, 3.80; N%, 15.30

Piperidinium 2-cinnamyl-6-cyano-8-metoxycarbonyl-7-[*p*-nitrophenyl]-5-oxo [1,2,4] triazolo[1,5-a]pyridinide 11f.

This compound was obtained in 54% yield, m.p. 252-253 ^{0}C (methanol); ir: 3000-2300 (br, b), 2200 (CN), 1700 (COO), 1650 (CO) cm^{-1}; ^{1}H-nmr: 1.56 (2H, m, CH_2 piperidinium), 1.63 (4H, m, $2CH_2$ pip.), 3.02 (4H, m, $2CH_2$ pip.), 3.45 (3H, s, CH_3O), 7.27 (1H, d, CH=, J= 16.2 Hz), 7.30-7.80 (8H, m, ArH, =CH), 8.30 (4H, m, ArH, NH_2).

Anal. Cald. For $C_{28}H_{26}N_6O_5$: C%, 63.90; H%, 4.95; N%, 15.95

Found: C%, 63.70; H%, 5.00; N%, 15.80

2-cinnamyl-6-cyano-8-metoxycarbonyl-7-[*p*-nitrophenyl]-5-oxo [1,2,4] triazolo [1,5-a]pyridine 12f.

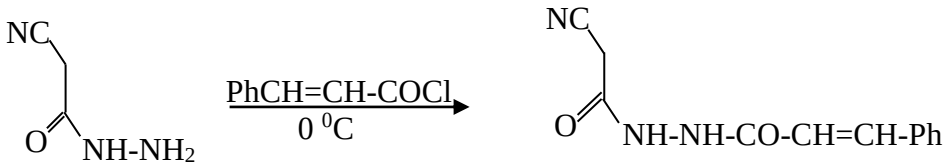
This compound was obtained in 22% yield, m.p. >325 ^{0}C (acetonitrile); ir: 3300-3000 (NH), 2220 (CN), 1700 (COO), 1650 (CO) cm^{-1}; ^{1}H-nmr: 3.51 (3H, s, CH_3O), 5.0 (1H, s , NH), 7.20-8.00 (9H, m, ArH, CH=CH), 8.39 (2H, m, ArH).

Anal. Cald. For $C_{23}H_{15}N_6O_5$: C%, 62.60; H%, 3.40; N%, 15.85

Found: C%, 62.40; H%, 3.55; N%, 15.60

Results and Discussion

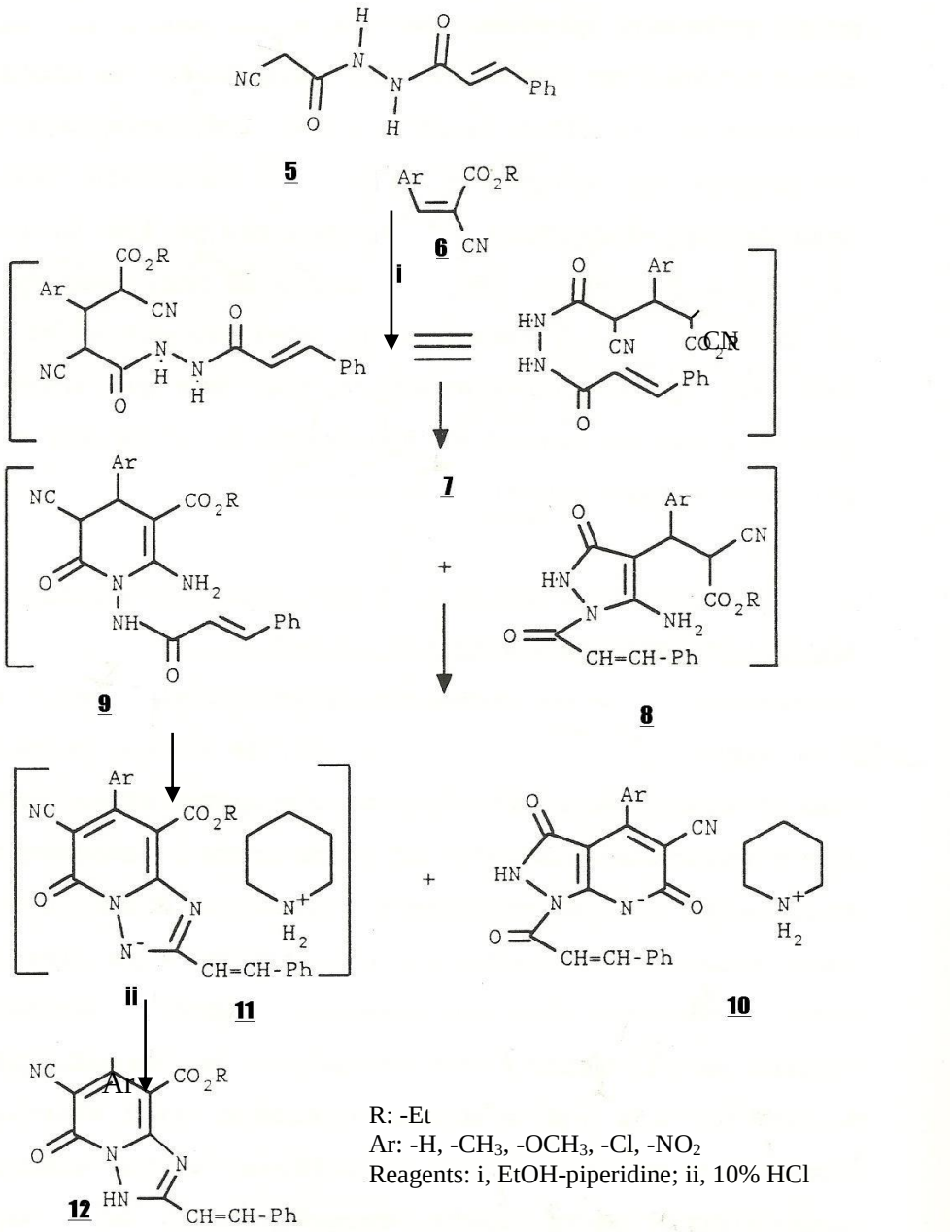
By the reaction of 2-cyanoacetohydrazide **1a** (scheme I) with 3-phenylpropenyl chloride at 0 ^{0}C, the corresponding 2′-Cinnamoyl-2-cyanoacetohydrazide **5** was formed in good yield.



1a **5**

(Scheme I)

As a part of our current program to study the group reactivity relationships for cyclization, we found that it is of interest to investigate the influence of replacing the alkoxycarbonyl for the cyano-group in the cinnamonitriles **6** led to a competitive cyclization to pyrazolo[3,4-b]pyridinides **10** as its piperidinium salt, and 7-aryl-2-cinnamyl-8-etoxycarbonyl [1,2,4] triazolo[1,5-a]pyridine **12** obtained from non-isolated intermediate piperidinium salt **11** by acid treatment (See scheme II).

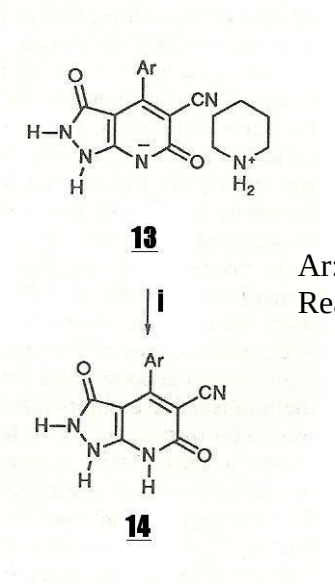


Scheme II

The Michael addition of the anion of the 2-cinnamoyl-2-cyanoacetohydrazide **5**, to the 2-etoxycarbonylcinnamonitriles **6** in alcoholic solution and in the presence of a stoicheiometric amount of piperidine at reflux temperature leads to the adducts **7**. The synthesis of compounds **12** involves the formation of the pyridine ring **9** by attack an amide nitrogen on a cyano group of the intermediate **7**, followed by a second cyclization leading to the five membered ring of the [1,2,4]triazolo[1,5-a]pyridinone **12**.

An alternative cyclization seems to be responsible for the formation of pyrazolo[3,4-b]pyridinides **10**, can be take place as depicted in (scheme II). Nucleophilic attack by a nitrogen at the cyano group through a *5-exo-dig* cyclization leading to the non-isolable aminopyrazole derivative **8** which undergoes a second *6-exo-dig* cyclization followed by a spontaneous aromatization to the corresponding pyrazol[3,4-b]pyridinone which was isolated as its piperidinium salt **10**, with cinnamoyl group attached to the nitrogen in position one (Scheme II).

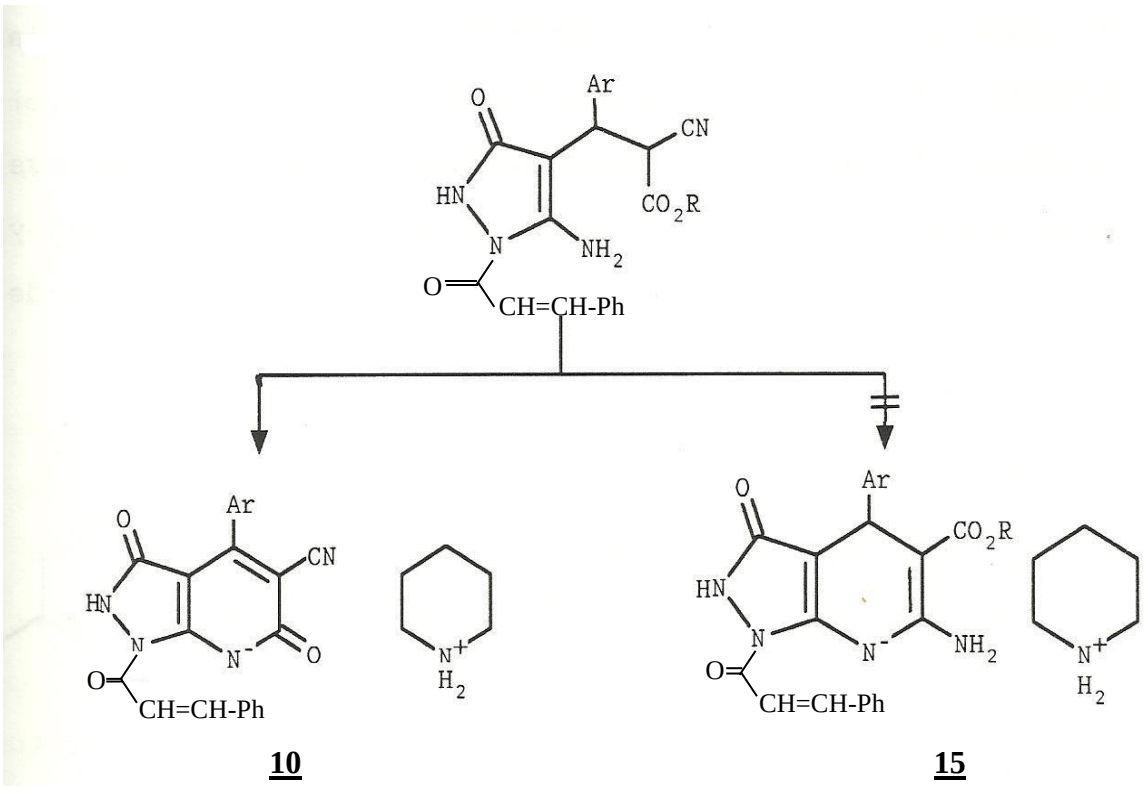
According to the general procedure the reaction of 2-alkoxycarbonylcinnamonitriles **6a** with 2-cinnamoyl-2-cyanoaceto-hydrazides **5** lead to the formation of piperidinium 5-cyano-3,6-dioxo-4-phenyl pyrazolo[3,4-b]pyridinides **13**, 25% yield [Ali *et al.*,1993a]. The presence of cinnamoyl group was not observed (Scheme III).



Ar: Ph
Reagents i: EtOH, Piperidine
10% HCl

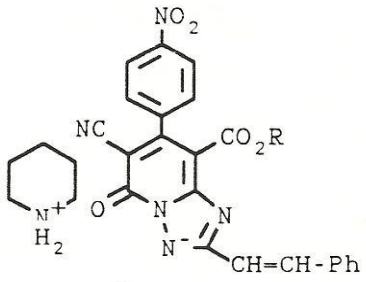
Scheme III

The other very important study in our current program the influence of both substituents in compound **6** and reaction temperature has been studied. It is worth mentioning that the alternative *6-exo-dig* cyclization in **8**, leading to the piperidinium pyrazolo[3,4-b] pyridinides **15** was not observed. This result is in contrast with previously reported synthesis of 1,6-diamino-2-pyridones [Aparicio, *et al.*, 1989)], in which the cyclizations by the cyano or carbonyl group were temperature controlled (Scheme IV).



(**Scheme IV**)

The new study to the presence of the nitro-group as the substituent in the benzene ring for the cinnamonitriles derivative **6e**, lead to the different interest in the current of the reaction. According to the general procedure the reaction of compounds **5** with **6** is not lead to the formation of pyrazolo[3,4-b]pyridine **10**, it is isolated only the [1,2,4]triazolo[1,5-a]pyridine as salt **11** with high yield. To the mother liquors was added 10% solution of hydrochloric acid which give the neutral compound **12** with low yield. The reaction is take place at room temperature or reflux. Formation of a complex mixture was observed from which only compound **11** resulting from the retro Michael reaction of the intermediate **7**. This reaction is happened due to the character of withdrawing electrons of nitro group which causes the retro Michael reaction of the intermediate **7**. (R: -Me or –Et, **6e**-Ar: -NO_2)



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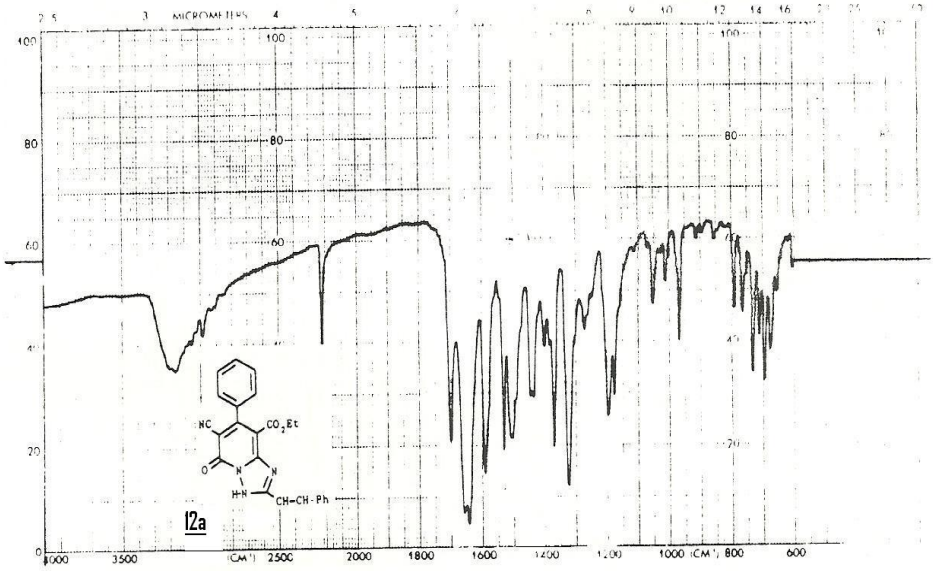
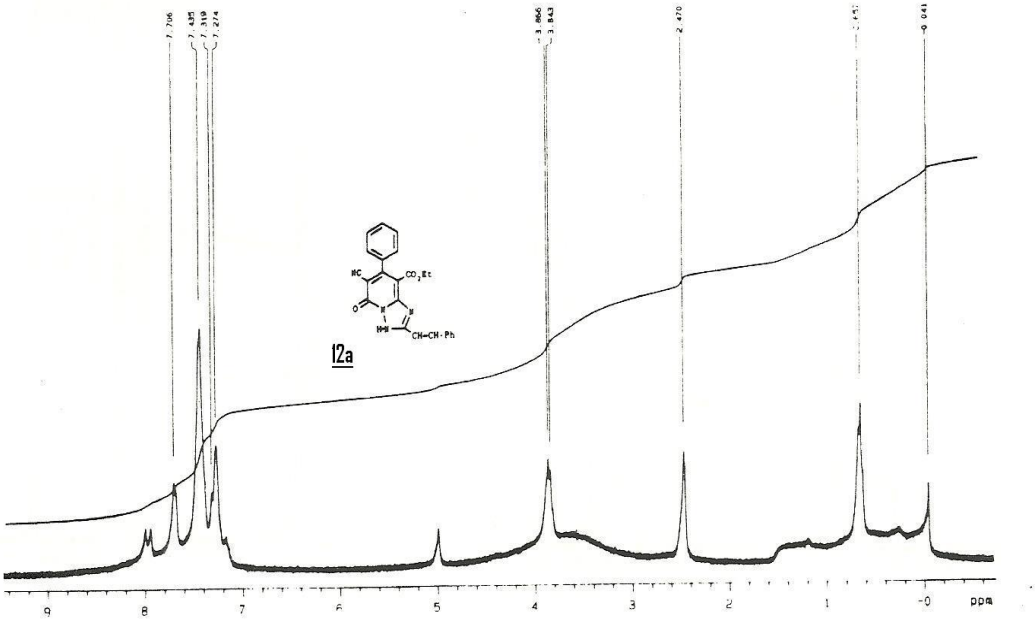
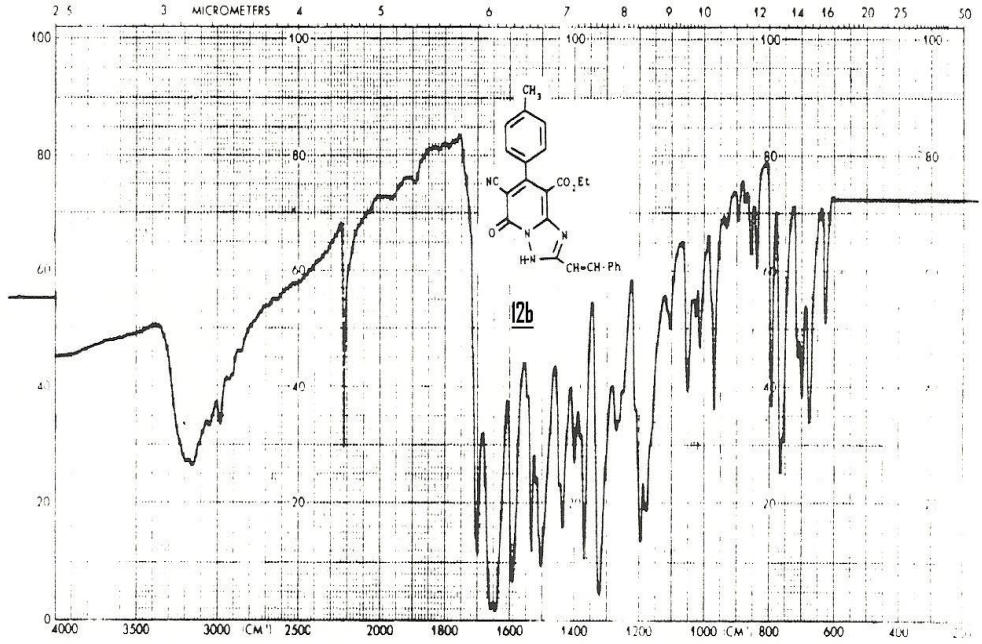
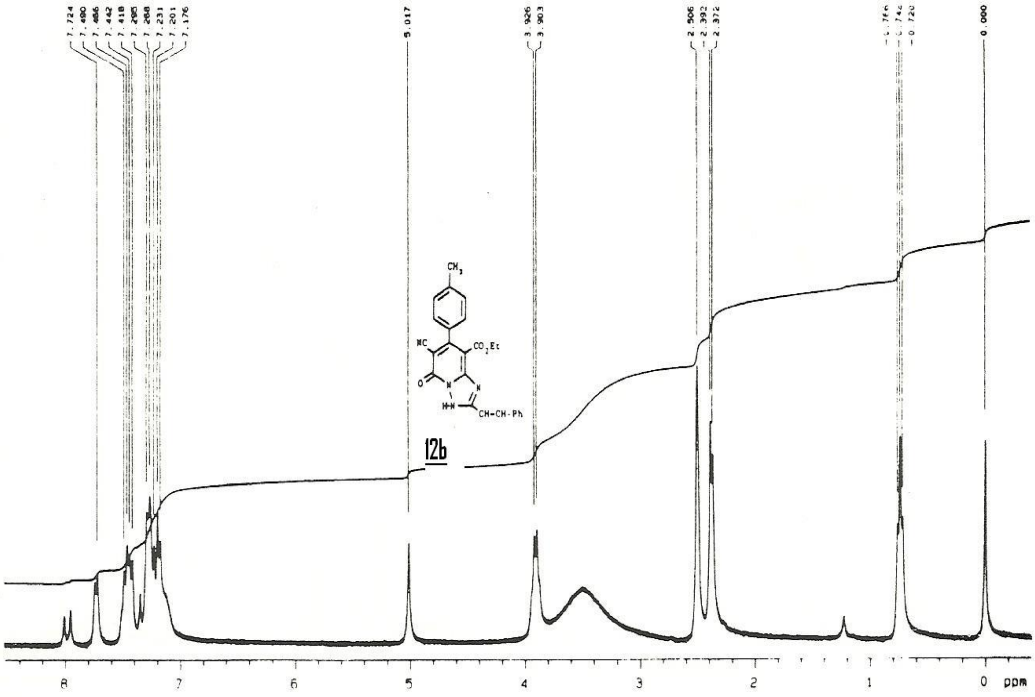
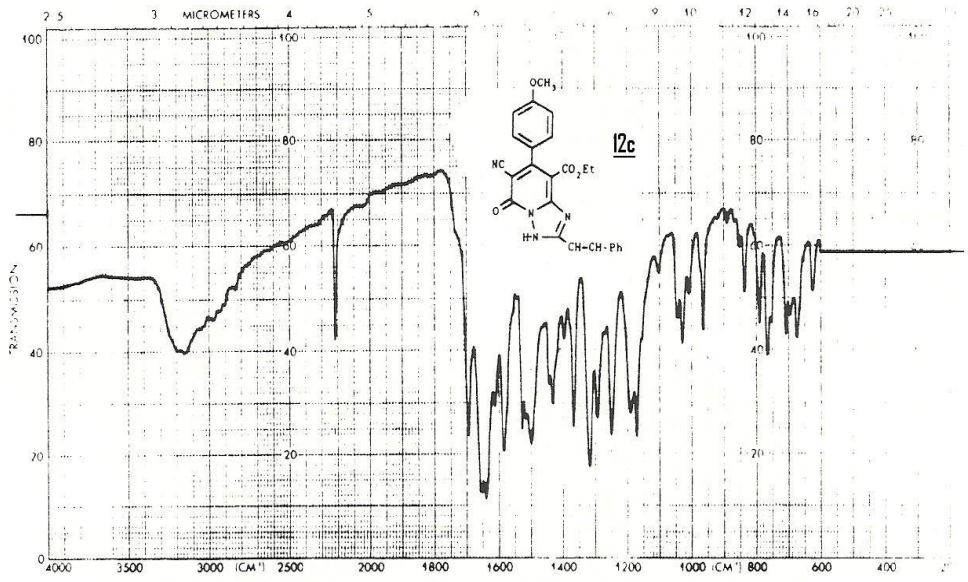
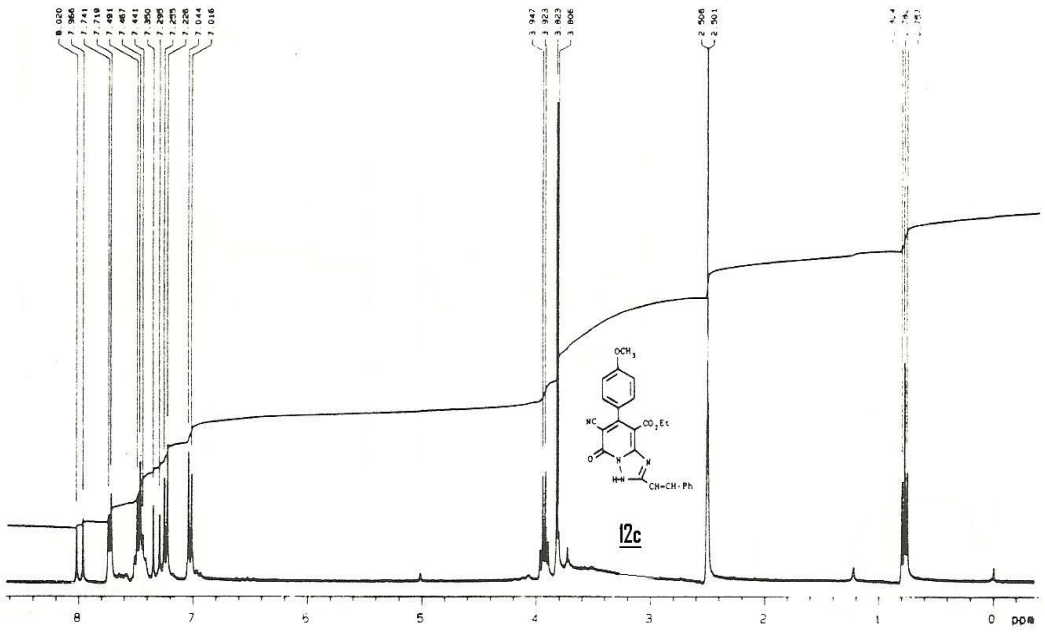

12a
CM⁻¹

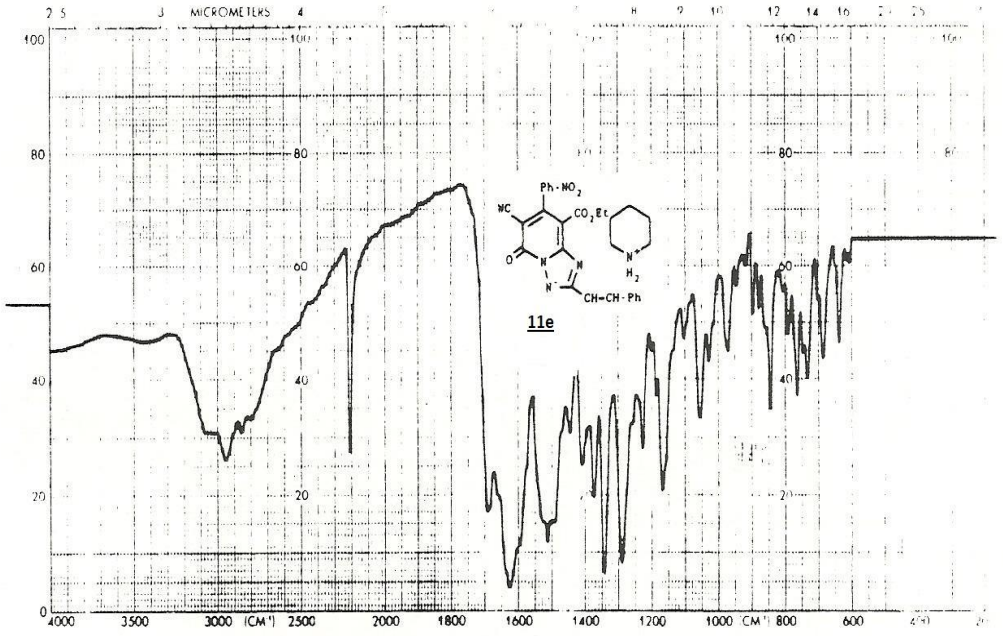

12a
ppm

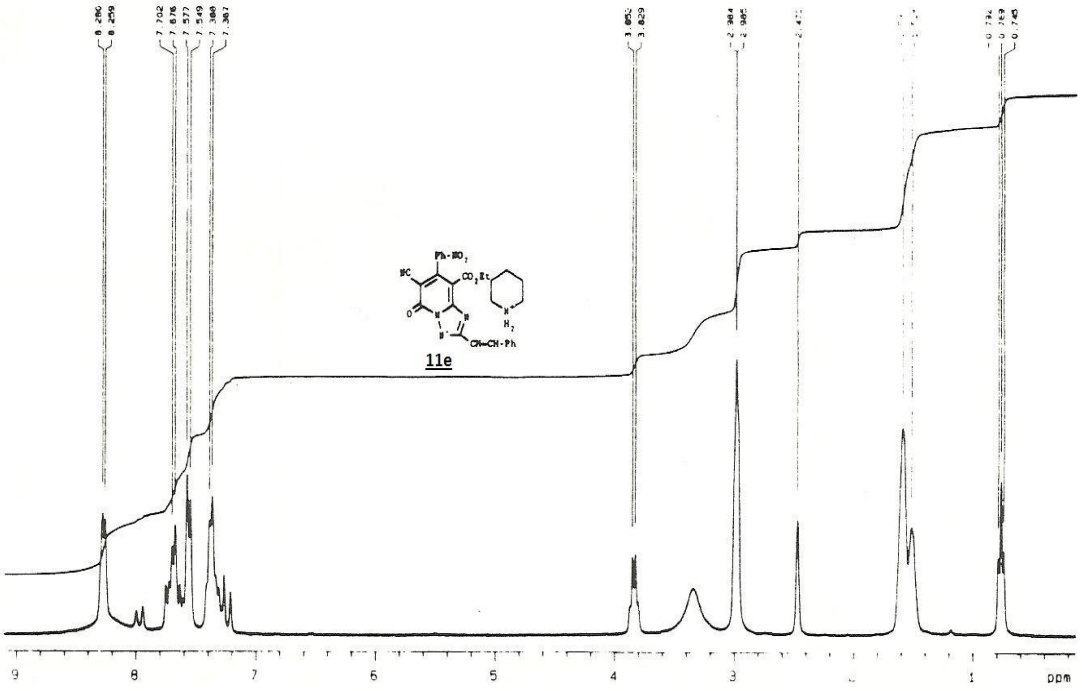

MICROMETERS
12b
(CM⁻¹)

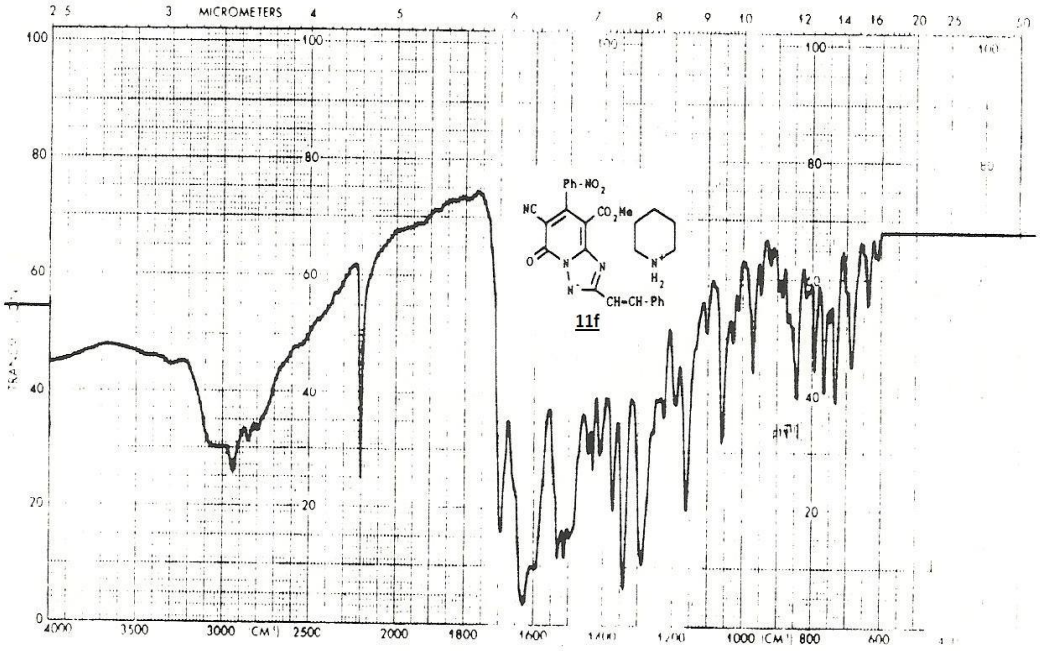

12b
ppm


MICROMETERS
TRANSMISSION
(CM⁻¹)
12c


12c
ppm


MICROMETERS
(CM⁻¹)
11e


11e
ppm


MICROMETERS
CM-1
11f


11f
ppm