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Reactivity of 2-metoxycarbonylcinnamonitriles with 2¯-Cinnamoyl-2-cyanoacetohydrazides Competitive cyclizations to piperidinium pyrazolo[3,4-b]pyridinides and 2-Cinnamyl[1,2,4]triazolo[1,5-a]pyridine

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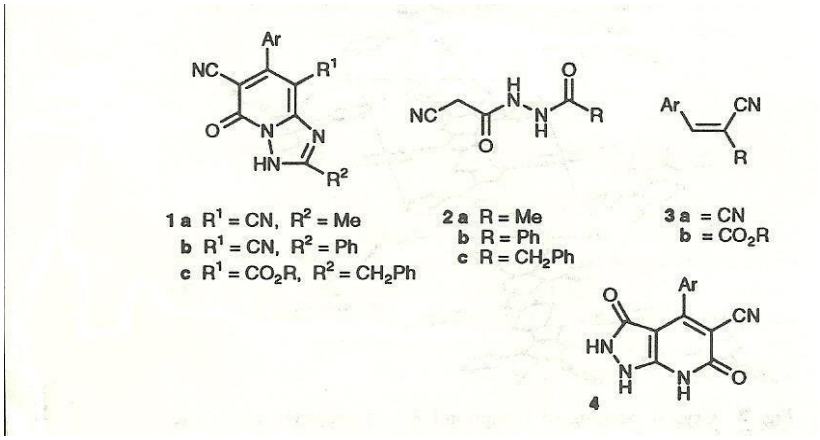
Abstract:

The reaction of 2-methoxycarbonylcinnamonitriles 6 and 2¯-cinnamoyl-2-cyano- aceto hydrazide 5 lead to the formation of a novel synthesis of piperidinium pyrazolo [3,4-b]pyridinides 10. In the reaction, an alternative cyclization leading to form 2-cinnamyl[1,2,4]triazolo[1,5-a]pyridine 12. Compounds 12 were isolated from the reaction mixture as the corresponding piperidinium salts 11 due to the high stability of the heterocyclic anion. Acidification with 10% of hydrochloric acid result the neutral 2-cinnamyl[1,2,4]triazolo[1,5-a]pyridine 12. The reaction is depending on the conditions, the corresponding intermediate dihydropyrid- inones 7 pyrazolo derivatives 8 were also obtained.

Introduction:

In the past papers [1,2,3], we known different methods for the preparative of [1,2,4]triazolo[1,5-a]pyridines involve: (a) the reaction of 2¯-acetyl-2-cyanoacetohydrazide, 2¯-benzoyl-2-cyanoaceto-hydrazide, or 2-cyano-2¯-phenylacetylacetohydrazide 2 with 2-cyano-cinnamonitriles 3. These reactions which are lead to the two roots, one of them led to the synthesis of 2-substituted [1,2,4]triazolo[1,5-a]pyridines 1 derivatives and the other root lead to preparation of 3-oxopyrazolo [3,4-b]pyridines 4 derivatives [1,2,3]. (b) A copper catalyzed reaction of pyridine derivatives [9]. (c) More of these compounds have been prepared by cycloaddition between *N*-aminomethyl-pyridinium and substituted benzonitriles in the presence of KOH at room temperature [14]. (d) These compounds have been prepared in good yield from aminopyridines [4]. (e) The comounds via reaction of arylidenemalononitriles with 2-[(substituted amino)thiocarbonyl]acetohydrazides, in refluxing ethanol , with presence of triethylamine [7]. These compounds have wide variety of applications such as pharmaceutics, complexing agent, or fluorescent brighteners [12].

The experimental method that leads to 1 as the piperidinium salt, from which compound 1 was generated by acidification. This method of acidification is a general method for application to liberate the neutral compound.



The introduction of the alkoxycarbonyl group instead of cyano group in the 2-substituted cinnamonitriles 3 which led to alternative cyclization to pyrazolo[3,4-b]pyridinones 4 which were also obtained, in a novel step, as the piperidinium salt that upon neutralization gave the neutral pyrazolo [3,4-b]pyridinones 4 [2,3]. The preparation of pyrazolo[3,4-b]pyridinones have attracted attention in recent years according to the wide variety of their biological and pharmalogical properties [6]. The methods described in the literature to prepare pyrazolo[3,4-b]pyridinones usually take place with several steps and, although some methods starting from the pyridine ring are known [8], most of them involve the construction of the pyrazole ring first, from which the pyrazolo[3,4-b]pyridinones is formed by subsequent cyclization [11].

The comparison between the previous compounds, the preparation presented here liberates the pyrazolo[3,4-b]pyridinone in one single step from easily available 2-cinnamoyl-2-cyanoacetohydra-zide 5 and 2-methoxycarbonylcinnamonitriles 6 in moderate to good yields. To the best of our knowledge, there is only one precedent in the literature in which a condensation of cyanoacetohydra-zide with 1,3-dicarbonyl compounds gave pyrazolo[3,4-b]pyridinones under certain conditions [14].

Experimental:

Melting point were determined in capillary tubes in a Electrothermal 9200 apparatus and are uncorrected. ^{1}H-nmr and ^{13}C-nmr spectra were recorded at 300 MHz and 75 MHz respectively 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. Mass spectra were obtained with a Varian MAT 711 machine, 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 [5].

2′-Cinnamoyl-2-cyanoacetohydrazide 5.

To a stirred solution of 2-cyanoacetohydrazide (1) (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

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

To a suspention of 2′-Cinnamoyl-2-cyanoacetohydrazide 5 (0.46 gm., 2mmol) and the corresponding arylidenecyanoacetate 6 (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-methoxycarbonyl-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-metoxycarbonyl-5-oxo-7-phenyl[1,2,4]triazolo[1,5-a] pyridine 12a.

This compound was obtained in 40% yield, m.p. 337-339 ^{0}C (acetonitrile); ir: 3300-3000 (NH), 2220 (CN), 1700 (COO), 1650 (CO) cm^{-1}; ^{1}H-nmr: 3.47 (3H, s, CH_3O), 5.01 (1H, s , NH), 7.2-7.9 (12H, m, ArH, CH=CH).

Anal. Cald. For $C_{23}H_{16}N_4O_3$: C, 69.70; H, 4.05; N, 14.15

Found: C, 69.90; H, 4.05; N, 14.00

Piperidinium 1-Cinnamoyl-5-cyano-4-(*P*-methylphenyl)-3,6-dioxopyrazolo [3,4-b] pyridinides 10b.

This compound was obtained in 25% yield, m.p. 266-268 ^{0}C (MeOH); ir: 3100 (NH), 3000-2300 (br.s), 2220 (CN), 1670 (CO-NH), 1650-1600 (CO) cm^{-1}; ^{1}H-nmr: 1.53 (2H, m, CH_2 pipridinium), 1.62 (4H, m , $2CH_2$ piperidinium), 2.45 (3H, s, CH_3), 3.09 (4H, m , $2CH_2$ piperidinium), 7.3 (2H, d, ArH) 7.4 (5H, m, ArH), 7.61 (2H, d, ArH), 7.63(1H, d, CH=), 8.02 (1H, d, =CH), 8.25 (2H, br.s, NH_2), 11.2 (1H, br.s, NH); ^{13}C-nmr: δ 20.05 (CH_3), 21.7 (C-γ, piperidinium), 22.3 (C-β, piperidinium), 43.90 (C-α, piperidinium), 86.64, 91.57 (C-3a, C-5), 118.93 (CN), 127.96 (2C), 128.15 (2C), 128.74 (2C), 128.99 (2C), 129.92, 130.76, 135.22, 138.72, 141.99 (ArH, CH=CH), 151.67, 158.4 (C-4, C-7a), 161.22, 161.84, 163.08 (3CO).

Anal. Cald for $C_{28}H_{27}N_5O_3$: C, 69.85; H, 5.35; N, 14.55

Found: C, 69.60; H, 5.60; N, 14.50

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

This compound was obtained in 50% yield, m.p. 345-347 ^{0}C (acetonitrile); ir: 3300-3100 (NH), 2220 (CN), 1700 (COO), 1650 (CO) cm^{-1}; ^{1}H-nmr: 2.34 (3H, s, CH_3), 3.46 (3H, s, CH_3O), 5.01 (1H, s , NH), 7.1-7.5 (8H, m, ArH, CH=), 7.7 (2H, d, ArH), 7.9 (1H, d, ArH).

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

Found: C, 69.95; H, 4.45; N, 13.55

Piperidinium 1-Cinnamoyl-5-cyano-4-(*P*-methoxyphenyl)-3,6-dioxopyrazolo [3,4-b] pyridinides 10c.

This compound was obtained in 23% yield, m.p. 265-267 ^{0}C (MeOH); ir: 3100 (NH), 3000-2300 (br.s), 2220 (CN), 1670 (CO-NH), 1650-1600 (CO) cm^{-1}; ^{1}H-nmr: 1.54 (2H, m, CH_2 pipridinium), 1.63 (4H, m , $2CH_2$ piperidinium), 3.02 (4H, m , $2CH_2$ piperidinium), 3.84 (3H, s, CH_3O), 7.1 (2H, d, ArH, J= 8.5 Hz), 7.42 (3H, m, ArH), 7.48 (2H, d, ArH, J= 8.5 Hz), 7.61(2H, m, ArH), 7.64 (1H, d, CH=, J= 16.2 Hz), 8.07 (1H, d, =CH, J= 16.2 Hz), 8.3 (2H, br.s, NH_2), 11.2 (1H, br.s, NH); ^{13}C-nmr: δ 21.86 (C-γ, piperidinium), 22.44 (C-β, piperidinium), 43.99 (C-α, piperidinium), 55.4 (CH_3o), 86.74, 91.57 (C-3a, C-5), 113.08 (2C), 119.31 (CN), 120.94, 125.58, 128.16 (2C), 129.18 (2C), 130.20, 130.77 (2C), 135.24, 142.41 (2ArH, CH=CH), 151.89, 158.32 (C-4, C-7a), 160.35 (ArH), 161.38, 162.08, 163.31 (3CO).

Anal. Cald for $C_{28}H_{27}N_5O_4$: C, 67.60; H, 5.45; N, 14.10

Found: C, 67.35; H, 5.50; N, 14.05

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

This compound was obtained in 56% yield, m.p. 327-329 ^{0}C (acetonitrile, DMSO); ir: 3300-3000 (NH), 2220 (CN), 1700 (COO), 1650 (CO) cm^{-1}; ^{1}H-nmr: 3.52 (3H, s, CH_3O), 3.82 (3H, s, CH_3O), 5.01 (1H, s , NH), 7.0-7.04 (2H, d, ArH), 7.20-7.33 (3H, m, ArH, CH=), 7.40-7.60 (3H, m, ArH), 7.70-8.06 (3H, m, ArH, CH=).

Anal. Cald. For $C_{24}H_{18}N_4O_4$: C, 67.60; H, 4.25; N, 13.15

Found: C, 67.40; H, 4.40; N, 13.30

Piperidinium 4-(*p*-Chlorophenyl)-1-cinnamoyl-5-cyano-3,6-dioxopyrazolo[3,4-b] pyridinides 10d.

This compound was obtained in 22% yield, m.p. 276-278 ^{0}C (MeOH); ir: 3100 (NH), 3000-2300 (br.s), 2220 (CN), 1690 (CO-NH), 1650-1550 (CO) cm^{-1}; ^{1}H-nmr: 1.53 (2H, m, CH_2 pipridinium), 1.62 (4H, m , $2CH_2$ piperidinium), 2.45 (3H, s, CH_3), 3.09 (4H, m , $2CH_2$ piperidinium 7.3 (2H, d, ArH) 7.4 (5H, m, ArH), 7.61 (2H, d, ArH), 7.63(1H, d, CH=), 8.02 (1H, d, =CH), 8.25 (2H, br.s, NH_2), 11.2 (1H, br.s, NH).

nal. Cald. For $C_{27}H_{24}ClN_5O_3$: C, 64.60.; H, 4.80; N, 13.95

Found: C, 64.55; H, 4.85; N, 13.95

7-(*p*-Chlorophenyl)-2-Cinnamyl-6-cyano-8-metoxycarbonyl-5-oxo[1,2,4] triazolo [1,5-a] pyridine 12d.

This compound was obtained in 56% yield, m.p. 347-349 ^{0}C (acetonitrile); ir: 3300-3000 (NH), 2220 (CN), 1740 (COO), 1690 (CO) cm^{-1}; ^{1}H-nmr: 3.50 (3H, s, CH_3O), 5.01 (1H, s , NH), 7.31 (3H,mArH), 7.40-7.55 (5H, m, ArH, CH=), 7.70 (2H, m, ArH), 7.95 (1H, d, =CH).

Anal. Cald. For $C_{23}H_{15}ClN_4O_3$: C, 64.10; H, 3.50; N, 13.00

Found: C, 63.85; H, 3.55; N, 12.80

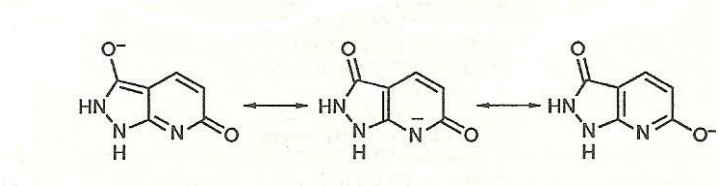
Results and Discussion:

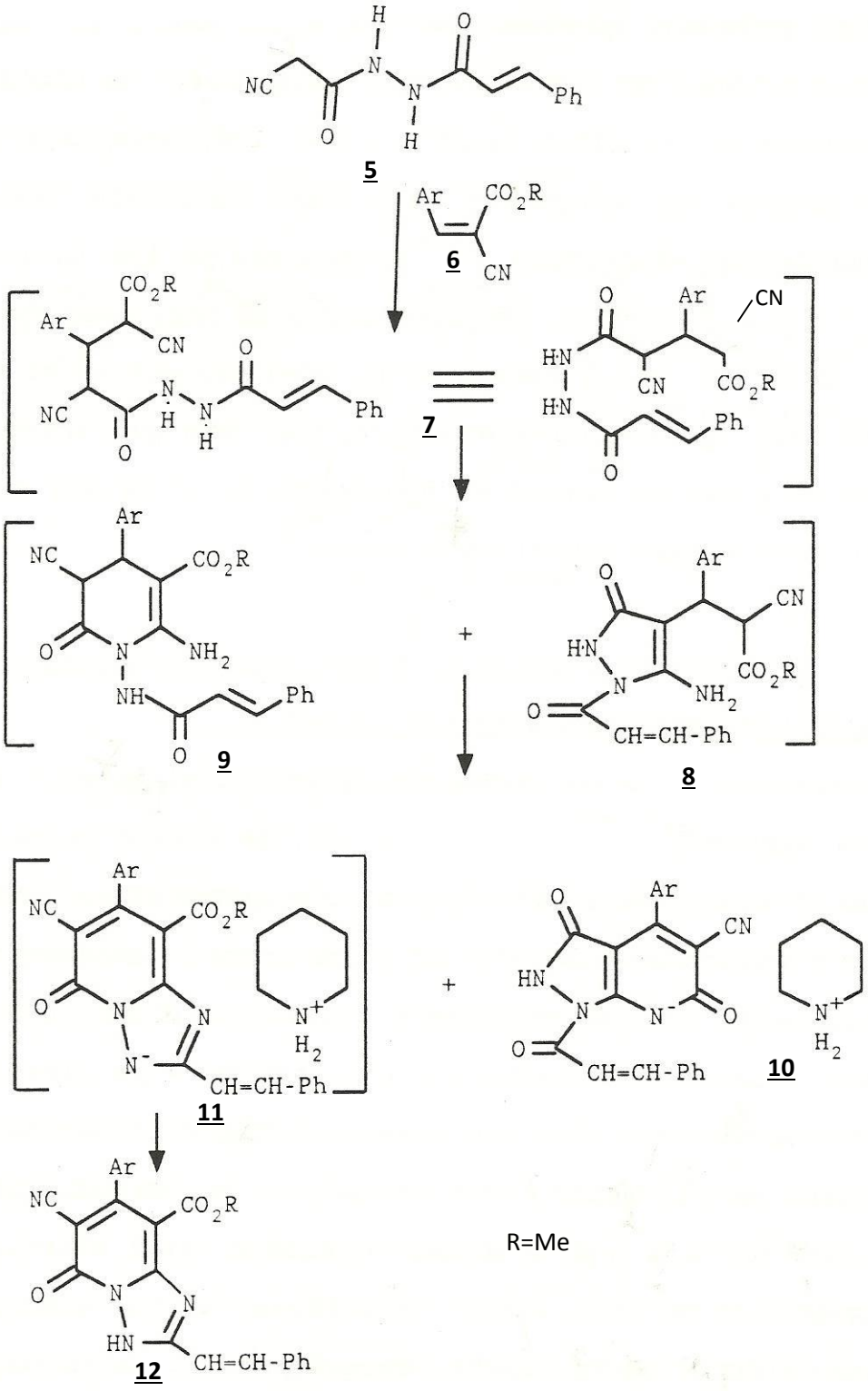
The preparation of the novel compounds 12a-d and 10b-d can be accounted for as depicted in scheme I, in which all the compounds obtained are shown. Thus, conjugate addition of 2$^-$-cinnamoyl-2-cyanoacetohydrazide 5 to 2-methoxycarbonylcinnamonitriles 6 in alcoholic solution and in the presence of a stoichiometric amount of piperidine at reflux temperature, afforded a mixture of pyrazolo [3,4-b]pyridinone, as its piperidinium salt 10 and 2-cinnamyl[1,2,4]triazolo[1,5-a]pyridine 12 resulted from the non-isolated intermediate

piperidinium salt 11 by acidification with 10% of hydrochloric acid solution. The process of the formation of the piperidinium salt 11 result from the construction of the pyridine ring 9 in *6-exo-dig* cyclization [10] from intermediate 7 and then led to the formation of piperidinium salt 11 by nucleophilic attack on the amide carbonyl group and spontaneous aromatization

An inverse order sequence seems to be responsible for the formation of piperidinium pyrazolo[3,4-b]pyridine 10. It can be rationalized from the common intermediate, adduct 7, by an alternative nucleophilic attack of the second amide nitrogen on the other cyano group in a compound 7 by a *5-exo-dig* process leading to the non-isolable aminopyrazole derivative 8 which undergoes a second *6-exo-trig* cyclization followed by spontaneous aromatization to the corresponding pyrazolo[3,4-b]pyridine which was isolated as its piperidinium salt 10. Formation of the compound 10 is accompanied by the presence of the cinnamoyl group attached to the nucleophilic nitrogen in intermediate 7.

Formation of the piperidinium salt in the triazolo[1,5-a]pyridinone is due to the anion's stability resulting from the charge delocalization involving the two triazolo nitrogens and the pyridine oxygen in compound 11. Stabilization of the anion in pyrazolo[3,4-b]pyridinone which was isolated as its piperidinium salt 10, involving a delocalization of the negative charge on the pyridine nitrogen and oxygen and the carbonyl oxygen on the five membered ring [13].





Scheme I

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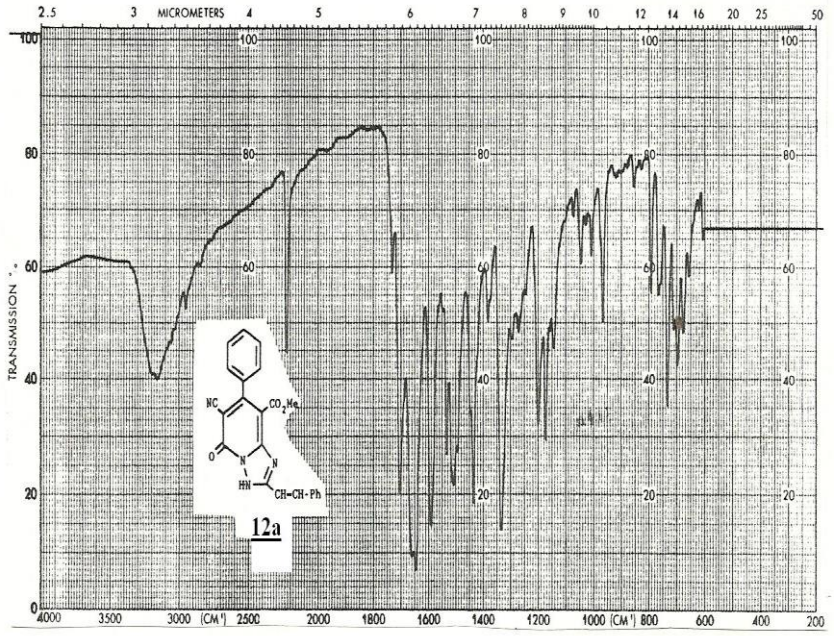
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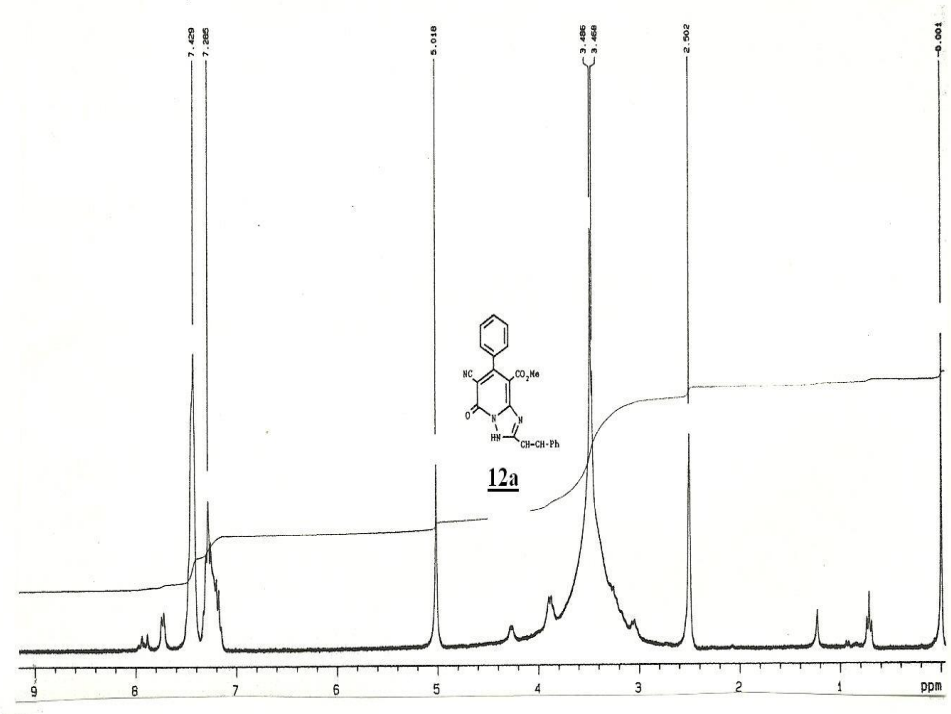
TRANSMISSION %
(CM⁻¹)
12a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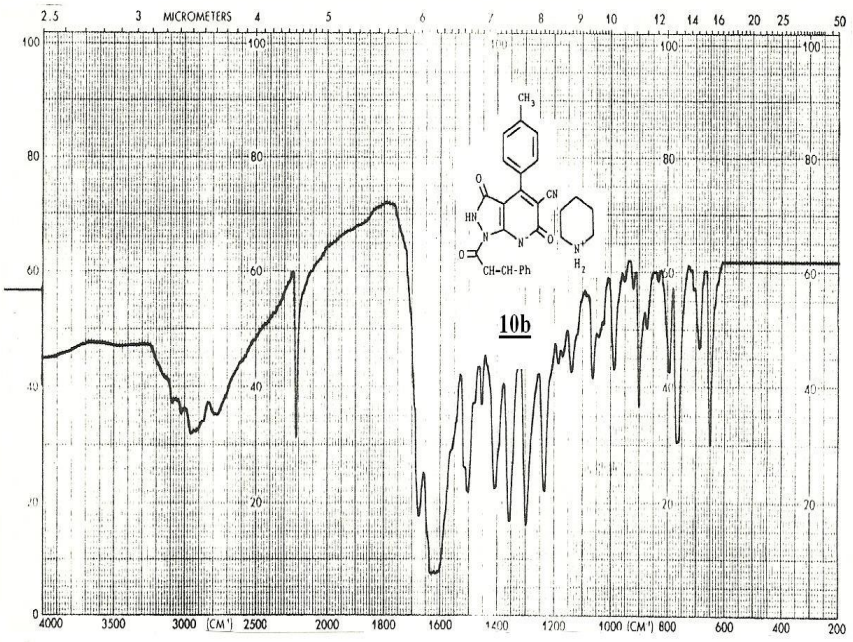
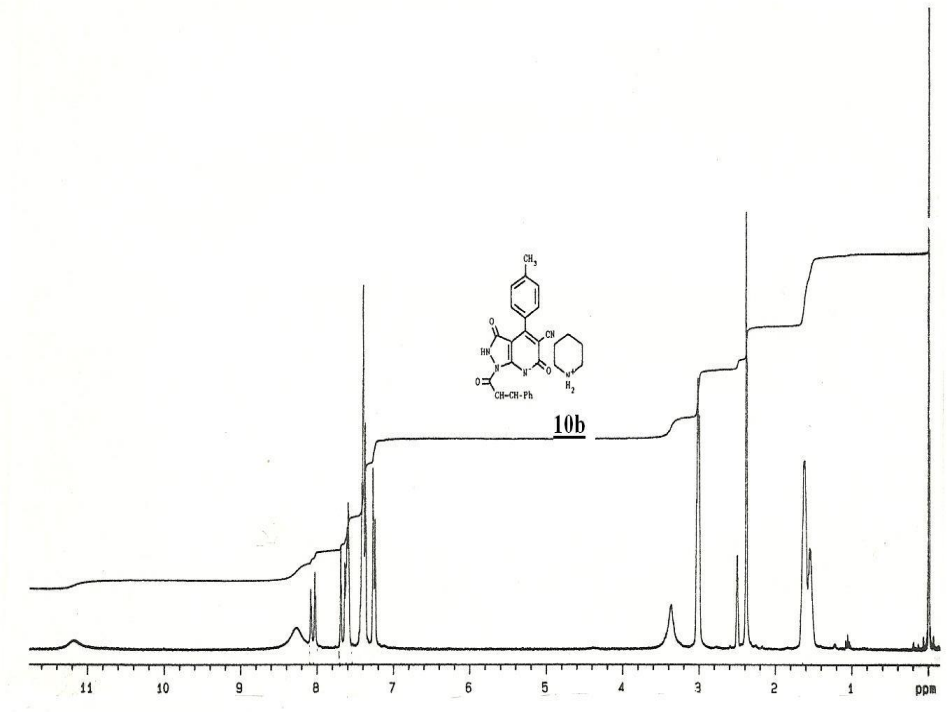
5.018
3.495
3.459
2.502
0.001
ppm
12a


MICROMETERS
CH-CH-Ph
10b
(CM⁻¹)


CH-CH-Ph
10b
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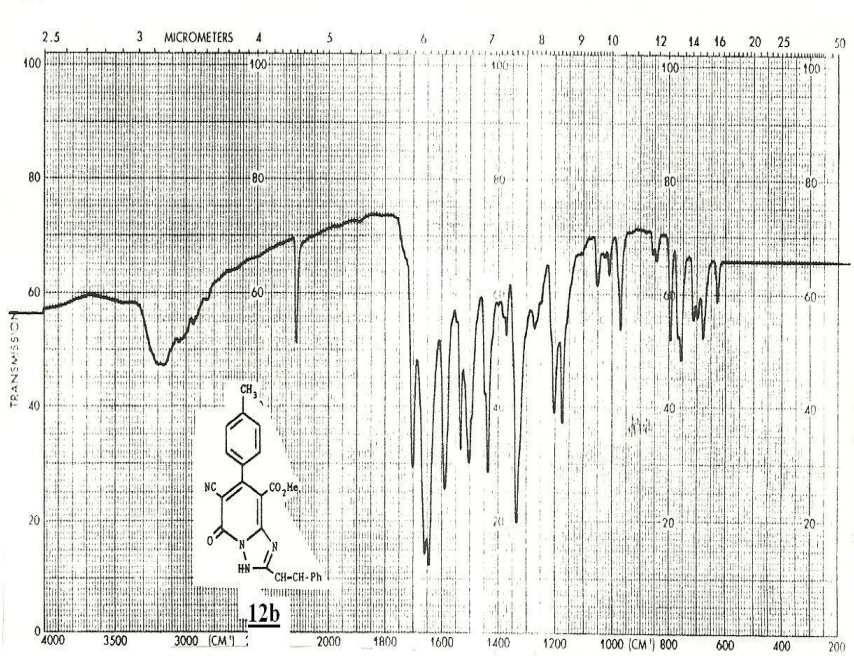
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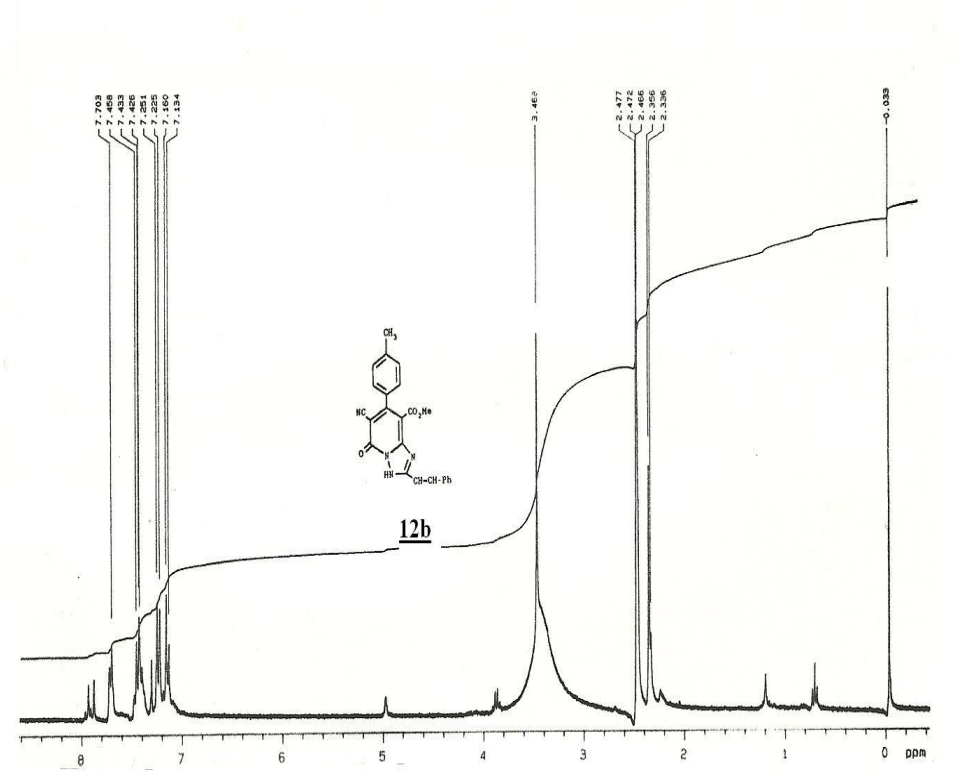
TRANSMISSION
12b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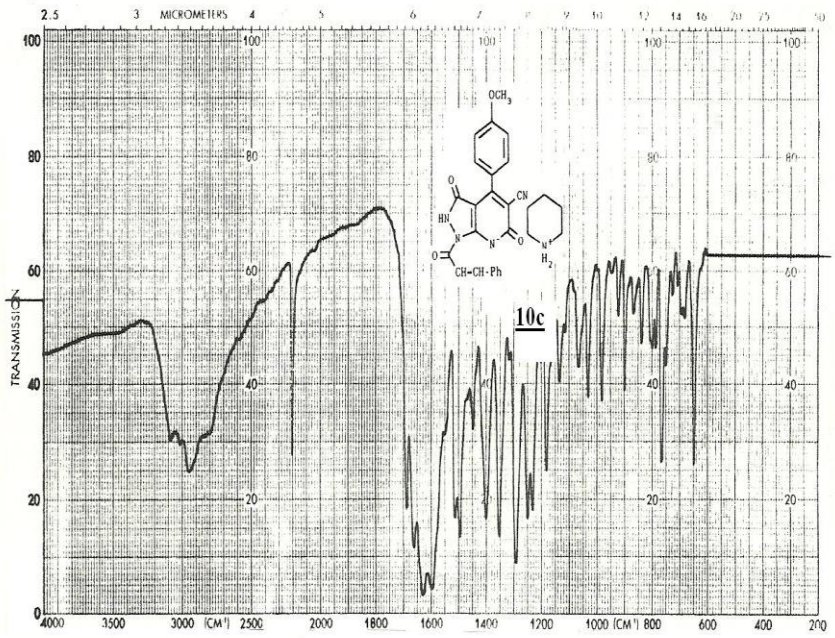
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3 MICROMETERS
4
TRANSMISSION
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3000 (CM-1)
2500
2000
1800
1600
1400
1200
1000 (CM-1)
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600
400
200
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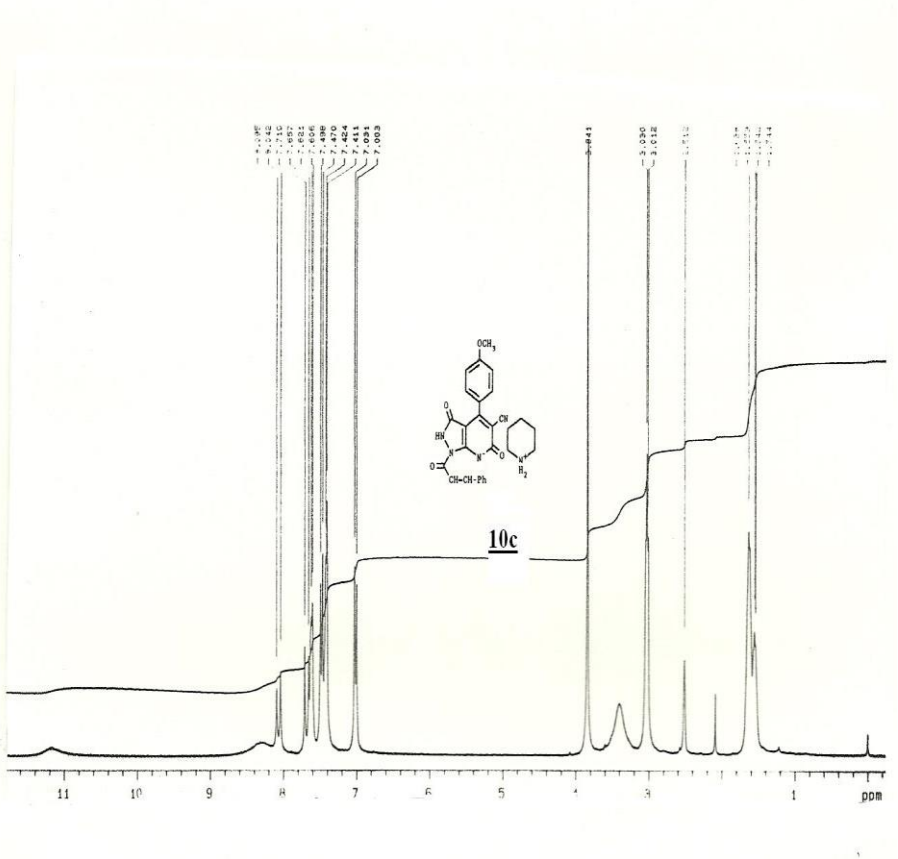
CN
HN
N
O
CH=CH-Ph
10c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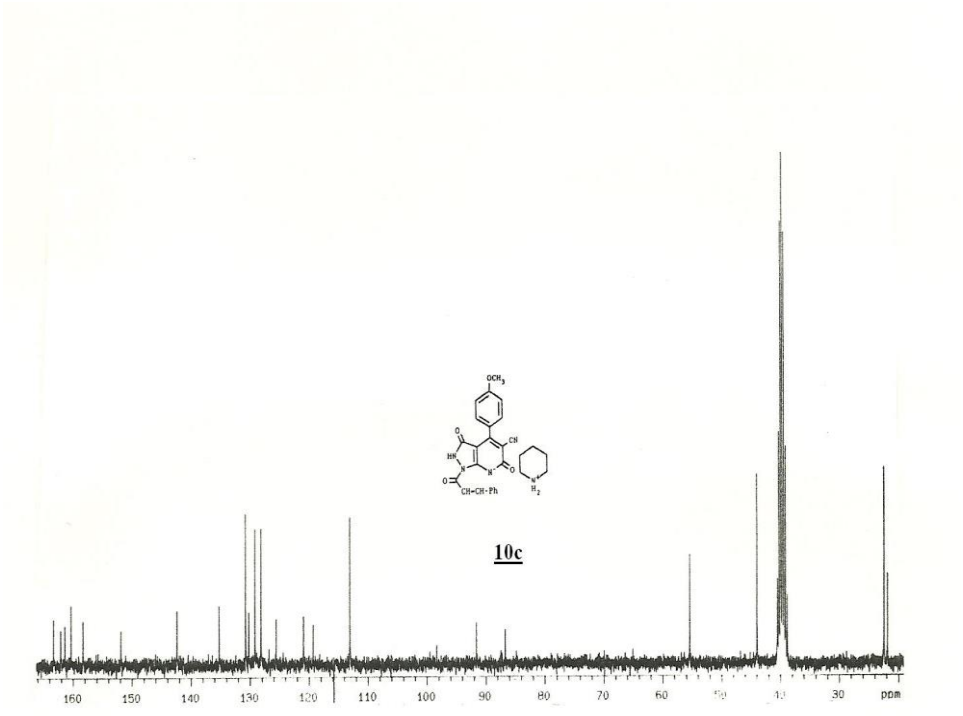
O
CH=CH-Ph
10c
11
10
9
8
7
6
5
4
3
1
ppm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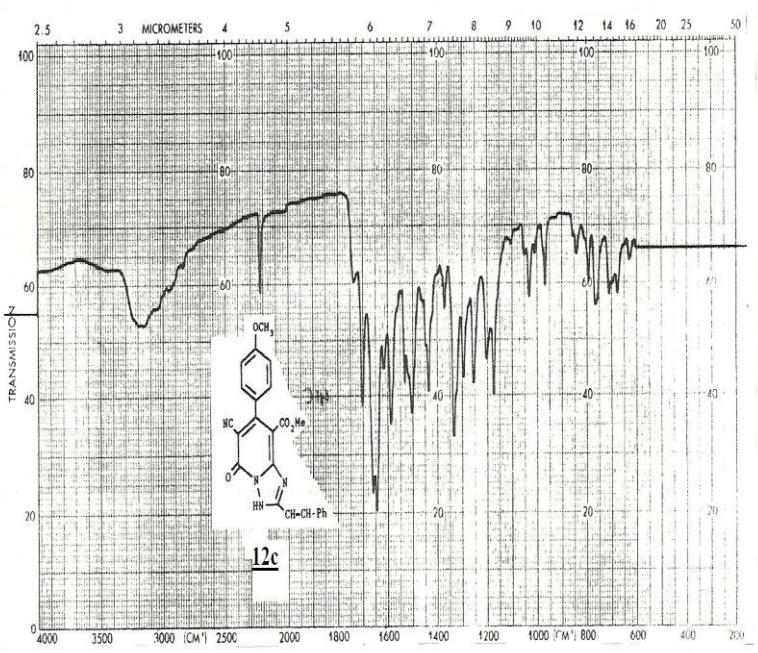
10c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1200
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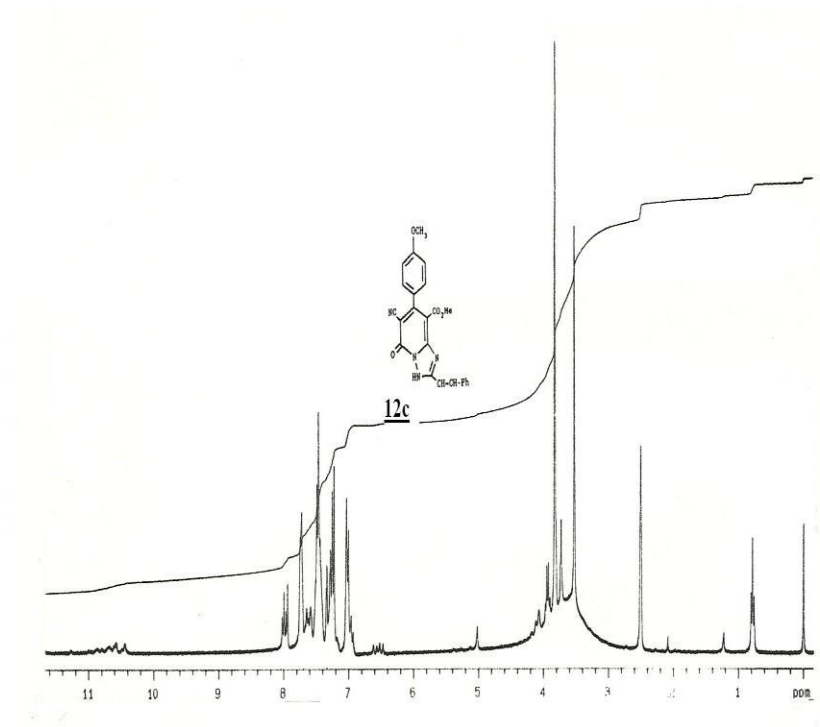
800
600
400

12c



دراسة فعالية تعويض ميثوكسي كاربونيل بدل مجموعة سيانو في المركب 3 لأنتاج المركب ببر دينيوم بريزول [3,4-b]بريدينيدس والمركب 2-سينا ميل[1,2,4]تريزول [1,5-a]بريدين

علي هادي

المعهد التقني/الكوفة- قسم الصيدلة

الخلاصة

الناتج الحاصل من تفاعل المركب 2-سينامويل-2-سيانوأسيتوهايدرازيد 5 مع المركب 2-ميثوكسي كاربونيل - سينامونتريل 6. هو تكوين مركبات حلقية جديدة مختلفة وهي ببري دي نيوم بي ريزولو [3,4-b] بري دي نيدس 10 وكذلك المركب 2-سينا ميل- 1,2,4] ترايزولو[1,5-a] برد ين 12. هذه المواد استخلصت املاح نتيجة الى أستقرار اللأ نيون الناتج من أ نتقال الشحنة السالبة بين ذرتي النايتروجين الموجودة في الحلقة الخماسية وكذلك ذرة الأوكسجين الموجودة في الحلقة السداسية. وعندة معاملة الرا شح مع محلول 10% من حامض الهايدروكلوريك تم الحصول على المركب 12 بشكل متعادل.