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3-아미노-1H-피라졸-4-카르복실산 에틸의 디아조화와 결합반응; 피라졸로아진의 합성

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Diazotization and Coupling Reactions of Ethyl 3-amino-1H-pyrazole-4-carboxylate; Synthesis of some Pyrazoloazines

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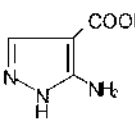
요 약. 피라졸로아진은 농업이나 의약품에서 매우 유용한 화합물들이다. 본 논문에서는 몇 가지 새로운 피라졸로아진의 합성을 보고하고자 한다. 표제 화합물인 3-아미노-1H-피라졸-4-카복실산 에틸을 다이아조화한 후 활성화된 메틸렌 화합물들과 반응시키고 고리화하여 피라졸로[5,1-*c*][1,2,4]트라이아진 유도체들을 합성하였다. 또한 표제 화합물을 α-치환된 신남나이트릴들과 반응시켜 피라졸로[1,5-*a*]피리미딘 유도체들을 합성하였다. 새로 합성된 화합물들의 구조는 화학적 방법과 분광학적 방법을 사용하여 확립하였다.

ABSTRACT. Pyrazoloazines are extremely useful in agriculture and medicine. The main objective of this article is to synthesize some new pyrazoloazines. Ethyl 3-amino-1H-pyrazole-4-carboxylate undergoes diazotization, couples with activated methylene compounds and cyclizes to form pyrazolo[5,1-*c*][1,2,4]triazine derivatives. The title compound also reacts with α-substituted cinnamonitriles to produce pyrazolo[1,5-*a*]pyrimidine derivatives. Structures of newly synthesized compounds are established via chemical and spectral methods.

Some pyrazoloazines are found to be useful in agricultural applications as herbicides and plant growth regulants[1], and in medicinal applications as antibiotics[2], antilipemics and cardiotonics[3], central nervous system agents[4], anxiolytics[5], treatment of influenza[6], antidepressants and antihypertensives[7], and its antileishmanial and antitrypanosomal activities[8]. Due to these agricultural and medicinal activities, it is desirable to synthesize novel heterocyclic compounds containing the pyrazole ring fused to either pyrimidine or 1,2,4-triazine rings.

The title compound (1) was prepared according to literature[9] and used as a starting material to synthesize the desirable azoloazines.



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Compound 1 was diazotized with hydrochloric acid and sodium nitrite then coupled with either phenolic compounds or some activated methylene nitriles. Thus, when the diazotized derivative of 1 was coupled with each of 2-naphthol or 8-hydroxyquinoline, it yielded the corresponding arylazo derivatives 2a,b, respectively (Scheme I). The IR spectra of compounds 2a,b displayed absorption bands near 3300 cm^{-1} (NH), 3200-2980 (broad OH) and 1710 (CO). The ^{1}H-NMR spectrum

(DMSO-d_6) of 2a, as an example, showed signals at δ 1.32 ppm (t, 3H, CH_3), 4.20 (q, 2H, CH_2), 6.71-8.60 (m, 7H, 6 aromatic protons + pyrazole H-5), 13.47 (s, 1H, NH, D_2O exchangeable) and 14.15 (s, 1H, OH, D_2O exchangeable).

Treatment of the produced diazonium salt with some activated methylene compounds, namely malononitrile, ethyl cyanoacetate and benzoylacetonitrile, yielded the corresponding azo derivatives 3a-c, respectively (*Scheme* 1). The IR spectra of 3a-c displayed absorption bands near 3400 cm^{-1} (NH), 2220 (CN), 1700 and 1670 (CO). The ^{1}H-NMR spectrum (DMSO-d_6) of compound 3b, as an example, showed signals at d 1.31 ppm (t, 3H, CH_3), 1.39 (t, 3H, CH_3), 4.30 (q, 2H, CH_2), 4.43 (q, 2H, CH_2), 8.30 (s, 1H, pyrazole H-5), 8.74 (s, 1H, NH, D_2O exchangeable) and 9.56 (s, 1H, NH, D_2O exchangeable). The mass spectrum of 3a showed the molecular ion peak at m z 232 (59.5%).

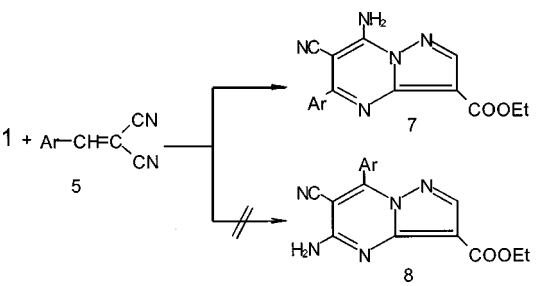
The mass spectrum of 3c showed the molecular ion peak at m z 311 (86.8%).

Heating under reflux compounds 3a-c with aqueous alcoholic potassium hydroxide solution led to the formation of the cyclised products ethyl 4-amino-3-substituted-pyrazolo[5,1-*c*][1,2,4]triazine-8-carboxylates (4a-c), respectively (*Scheme* 1).

Formation of 4 from 3 most probably took place via Michael-type addition of the pyrazole NH on the cyano group. The IR spectra of compounds 4a-c revealed the absence of any absorption bands in the cyano region, as well as the appearance of the expected NH and CO bands. It seems that 3a underwent partial hydrolysis to convert the cyano group into amide group.

The mass spectrum of 4b showed the molecular ion peak at m/z 280 (47.0%).

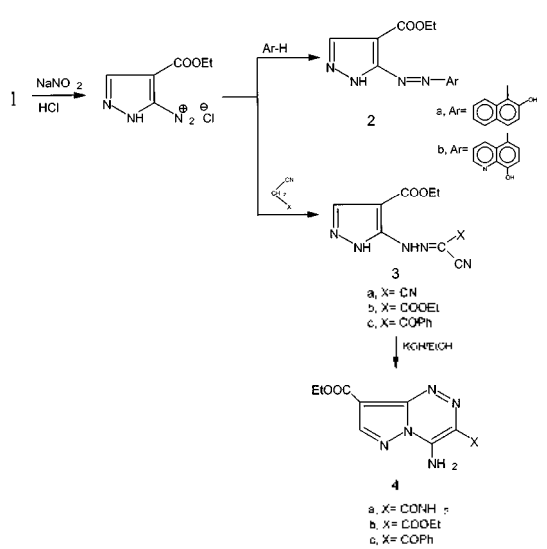
Furthermore, compound 1 behaved differently towards some α-substituted cinnamonitriles (5a,b & 6a,b), when a solution of 1 was heated under reflux with 5 or 6 in pyridine. Thus, when compound 1 was treated with a solution of each of the α-cyanocinnamonitriles 5a,b in pyridine, ethyl 7-amino-5-aryl-6-cyanopyrazolo[1,5-a]pyrimidine-5-carb-oxylates (7a,b), rather than the isomeric compounds 8a,b, was produced.



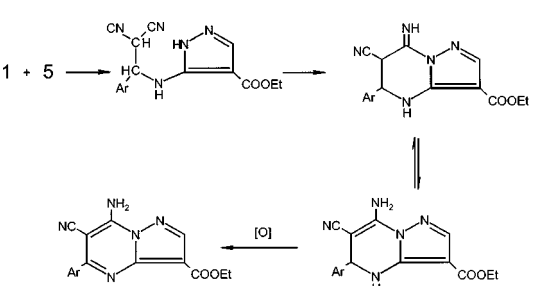
a, Ar = C_6H_5
b, Ar = C_6H_4-Cl-p

Formation of 7 from 1 may proceed via firstly Michael addition of the amino group of 1 onto the ethylenic double bond of 5, secondly, addition of the pyrazole hydrogen atom onto the cyano group of the intermediate and finally autoxidation (*Scheme* 2).

Elemental analyses and IR data are in agreement with the proposed structures 7(8), experimental. The ^{1}H-NMR spectrum (DMSO-d_6) of 7a(8a), as an example, showed



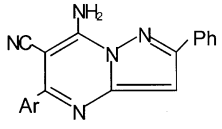
Scheme 1.



Scheme 2.

signals at δ 1.31 ppm (t, 3H, CH_3), 4.27 (q, 2H, CH_2), 7.60 (m, 3H, aromatic protons), 7.86 (m, 2H, aromatic protons), 8.61 (s, 1H, CH pyrazole) and 9.17 (bs., 2H, NH_2, D_2O exchangeable). The NH_2 signal appeared at δ 9.17 ppm, which favours the enaminonitrile moiety in structure 7b.

It seems that the proton NMR data are valuable in preferring 7 than 8. Thus in structure 7 the amino group should be affected by the both inductive and mesomeric effects of the cyano group (a structure which is known to show the chemical shift of the amino group at low field). Had we had structure 8 for the reaction product, the amino group should be affected by the electron withdrawal effect of the cyano group by inductive effect only. To some extent, similar work was reported by the research group, which I am a member of[10]. In this publication structures 9 and 10 similar to 7 and 8 were reported and showed that the amino group in 9 appeared at lower field than 10.



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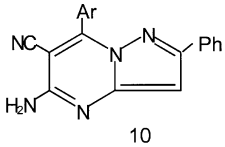

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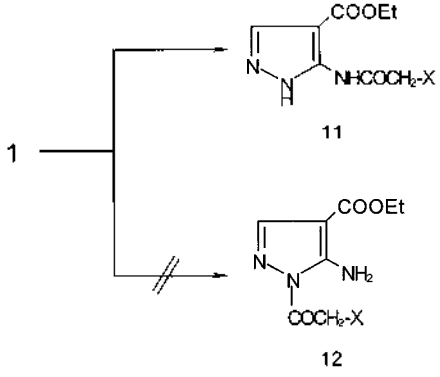
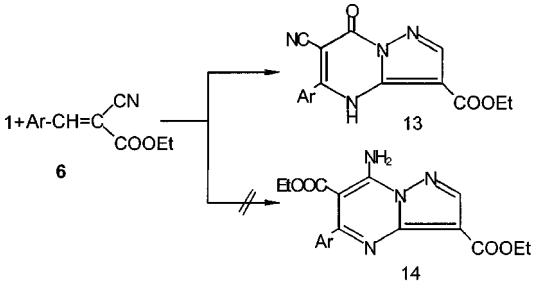
Moreover, an indirect chemical proof supporting the above structure 7 for the reaction product was performed. Acylation of compound 1 with acetic anhydride or chloroacetyl chloride gave, in each case, a monoacylated compound 11 with two different exchangeable NH protons. Thus, the presence of two different exchangeable protons in ^{1}H-NMR spectra of both 11a,b indicates that the acylation took place at the amino group and this in turn indicates that the amino group is more active towards electrophiles than the pyrazole NH group. That the reaction of 1 with some electrophiles starts at the amino group is in favor of structure 7.



a; X = H
b; X = Cl

On the other hand, heating compound 1 under reflux in pyridine with each of the ethyl α-cyanocinnamates (6a,b) led to the formation of the corresponding ethyl 5-aryl-6-cyano-7-oxo-4H,7H-pyrazolo[1,5-*a*]-pyrimidine-3-carboxylates (13a,b), respectively, rather than structure 1



a, Ar = C_6H_5
b, Ar = C_6H_4-Cl-p

Structure 13 was preferred over structure 14 on the basis of IR and mass spectra. Thus, the IR spectrum of the reaction product displayed absorption band at 2230 cm^{-1} (CN). Had we had structure 14 for the reaction product, it would not display any absorption at this region.

The mass spectrum of compound 13b showed the molecular ion peak at m\z 342 (100%) and 344 (34.2%).

EXPERIMENTAL

All melting points are uncorrected. IR spectra were recorded (KBr) on a Pye Unicam SP-1000 spectrophotometer. ^{1}H-NMR spectra were obtained with a Varian ^{1}H-Gemini 200 spectrometer with chemical shifts are expressed in δ (ppm) using TMS as the internal reference. Mass spectra were recorded on GC-MS QP 1000 EX mass spectrometer operating at 70 eV. The elemental analyses were performed by the Microanalytical Data Center, Cairo University, Egypt.

Ethyl 3-amino-1H-pyrazole-4-carboxylate 1

Was prepared as previously described[9].

Ethyl 3-arylazo-1H-pyrazole-4-carboxylate 2a,b

A Solution of 1 (0.775 g, 0.005 mol) in concentrated hydrochloric acid (5 ml) was cooled at 0°C and a cooled solution of sodium nitrite (0.8 g, 0.008 mol) in water (4 ml) was gradually added (15 min). The diazotized solution was coupled with 0.005 mol of both 2-naphthol (0.720 g) and 8-hydroxyquinoline (0.725 g) in ethanol containing two pellets of potassium hydroxide, kept at 0-5°C for 2 hours and diluted with water whereupon precipitation took place. The solid that precipitated in each case were collected and crystallized from dilute DMF.

Ethyl 3-[2-hydroxynaphth-1-ylazo]-1H-pyrazole-4-carboxylate 2a: Yield, 1.15 g (74.2%), m.p. 215°C; IR: 3417 cm^{-1} (NH), 3170-2990 (broad OH) and 1710 (CO). ^{1}H-NMR (DMSO-d_6): δ 1.32 ppm (t, 3H, CH_3), 4.20 (q, 2H, CH_2), 6.71-8.60 (m, 7H, 6 aromatic protons+pyrazole H_5), 13.47 (s, 1H, NH, D_2O exchangeable) and 14.15 (s, 1H, OH, D_2O exchangeable).

Analysis: $C_{16}H_{14}N_4O_3$ (310.309)

Required: C, 61.93; H, 4.54; N, 18.05%

Found: C, 62.0; H, 4.5; N, 18.1%

Ethyl 3-[8-hydroxyquinolin-5-ylazo]-1H-pyrazole-4-carboxylate 2b: Yield 1.20 g (77.4%); m.p. 206°C; IR: 3300 cm^{-1} (NH), 3200-2980 (broad OH) and 1708 (CO). ^{1}H-NMR (DMSO-d_6): δ 1.35 ppm (t, 3H, CH_3), 4.28 (q, 2H, CH_2), 7.36-8.91 (m, 6H, 5 aromatic protons pyrazole H_5), 12.55 (s, 1H, NH, D_2O exchangeable) and 13.95 (s, 1H, OH, D_2O exchangeable).

Analysis: $C_{15}H_{13}N_5O_3$ (311.296)

Required: C, 57.87; H, 4.21; N, 22.49%

Found: C, 57.9; H, 4.2; N, 22.4%

Coupling of 1with active methylene compounds; Preparation of 3a-c

The same experimental procedure described above for the synthesis of 2a,b has been followed up except for using the diazotized solution which coupled with active methylene compounds such as malononitrile, ethyl cyanoacetate and benzoyl acetonitrile in ethanol containing catalytic amount of sodium acetate, kept at 0°C for one hour and diluted with water whereby the solid product that precipitated in each case was filtered off, dried and crystallized from the proper solvent (cf. Table 1).

Ethyl 4-amino-3-substitutedpyrazolo[5,1-c][1,2,4]triazine-8-carboxy-lates 4a-c

To an aqueous ethanolic potassium hydroxide prepared by dissolving potassium hydroxide (0.3 g, 0.005 mol) in ethanol containing few drops of water, each of 3a-c (0.005 mol) was added and the solution was refluxed for 10 hours. The reaction mixture was then cooled, poured onto ice water acidified by hydrochloric acid, whereby, the solid that formed was filtered off, dried and crystallized from the proper solvent (cf. Table 1).

Ethyl 7-amino-5-aryl-6-cyanopyrazolo[1,5-a]pyrimidine-3-carboxy-late 7a,b

A mixture of 1 (0.005 mol) and some α-cyanocinnaminonitriles 5a,b was heated in pyridine under reflux for 24 hours. The reaction mixture was cooled and acidified with dilute hydrochloric acid, whereby, the solid that precipitated was filtered off, dried and crystallized from ethanol.

Ethyl 7-amino-5-phenyl-6-cyanopyrazolo[1,5-a]pyrimidine-3-carboxylate 7a: Yield, 1.18 g (77.12%), m.p. 250°C; IR: 3425 cm^{-1} (NH_2), 2243 (CN) and 1718 (CO). ^{1}H-NMR (DMSO-d_6): δ 1.31 ppm (t, 3H, CH_3), 4.27 (q, 2H, CH_2), 7.60 (m, 3H, aromatic protons), 7.86 (m, 2H, aromatic protons), 8.61 (s, 1H, pyrazole H_2), and 9.17 (bs, 2H, NH_2, D_2O exchangeable); mass spectrum at m/z 307 (42.6%).

Analysis: $C_{16}H_{13}N_5O_2$ (307.20)

Required: C, 62.55; H, 4.26; N, 22.79%

Found: C, 62.4; H, 4.2; N, 22.8%

Ethyl 7-amino-5-[4-chlorophenyl]-6-cyanopyrazolo [1,5-a]pyrimidine-3-carboxylate 7b:

Yield, 1.42 g (83.13%), m.p. 264°C; IR: 3307 cm^{-1} (NH_2), 2208 (CN) and 1697 (CO).

Analysis: $C_{16}H_{12}ClN_5O_2$ (341.75)

Required: C, 56.23; H, 3.53; Cl, 10.37; N, 20.49%

Found: C, 56.2; H, 3.6; Cl, 10.4; N, 20.5%

Ethyl 3-(N-acetylamino)-2H-pyrazole-4-carboxylate 11a: A solution of 1 (0.005 mol) in glacial acetic acid (5 ml) was treated by acetic anhydride (0.005 mol) and heated under reflux for 3 hours. The reaction mixture was diluted with cold water. The precipitate, that formed, was collected by filtration, dried and crystallized from ethanol to yield 0.76 g (77.55%) of 11a; m.p. 214°C; IR: 3342 cm^{-1} (NH), 3249 (NH), 1701 (CO) and 1681 (CO). ^{1}H-NMR (DMSO-d_6): δ 1.26 ppm (t, 3H, CH_3), 2.13 (s, 3H, CH_3), 4.21 (q, 2H, CH_2), 7.96 (s, 1H, pyrazole H-5), 9.90 (s, 1H, NH, D_2O exchangeable) and 13.21 (s, 1H, NH, D_2O exchangeable).

Analysis: $C_8H_{11}N_3O_3$ (197.19)

Table 1. Characterization Data of 3a-c and 4a-c

Comp. No.	M.p. (°C) (Solvent)	Yield (%)	Molecular Formula (M.Wt)	Analysis (Req/found) %C %H %N		IR (cm^{-1}) Selected bands
				%C	%H %N	
3a*	277 (AcOH)	82.75	$C_9H_8N_6O_2$ (232.19)	46.55 3.47 36.19	46.6 3.4 36.2	3417 (NH), 2229(2CN), 1697 (CO)
3b**	204 (EtOH)	89.92	$C_{11}H_{13}N_5O_4$ (279.25)	47.31 4.69 25.07	47.2 4.6 25.1	3514(NH), 2233 (CN), 1701-1697 (2CO)
3c***	175 (EtOH/H_2O)	74.19	$C_{15}H_{13}N_5O_3$ (311.29)	57.87 4.21 22.49	57.9 4.2 22.5	3161(NH), 2219(CN), 1687-1633 (2CO)
4a#	286 (DMF/H_2O)	77.66	$C_9H_{10}N_6O_3$ (250.21)	43.20 4.02 33.58	43.1 4.0 33.6	3375-3226 (NH_2), 1720-1695 (2CO)
4b##	221 (EtOH)	82.01	$C_{11}H_{13}N_5O_4$ (279.25)	47.31 4.69 25.07	47.2 4.7 25.1	3359-3280 (NH_2), 1703-1629 (2CO)
4c###	220 (EtOH)	83.22	$C_{15}H_{13}N_5O_3$ (311.29)	57.87 4.21 22.49	57.9 4.2 22.4	3246-3211 (NH_2), 1732-1683 (2CO)

*^{1}H-NMR (DMSO-d_6): δ1.33 ppm (t, 3H, CH_3), 4.25 (q, 2H, CH_2), 7.96 (s, 1H, pyrazole H_5), 8.65 (s, 1H, NH, D_2O exchangeable) and 10.89 (s, 1H, NH, D_2O exchangeable); mass spectrum at m/z 232 (59.5%).

**^{1}H-NMR (DMSO-d_6): δ1.13 ppm (t, 3H, CH_3), 1.39 (t, 3H, CH_3), 4.30 (q, 2H, CH_2), 4.43 (q, 2H, CH_2), 8.30 (s, 1H, pyrazole H-5), 8.74 (s, 1H, NH, D_2O exchangeable) and 9.56 (s, 1H, NH,D_2O exchangeable).

***^{1}H-NMR (DMSO-d_6): δ1.39 ppm (t, 3H, CH_3), 4.28 (q, 2H, CH_2), 7.48-8.27 (m, 6H, 5 aromatic protons+pyrazole H_5), 8.80 (s, 1H, NH, D_2O exchangeable) and 11.05 (s, 1H, NH, D_2O exchangeable); mass spectrum at m/z 311(86.8%).

#^{1}H-NMR (DMSO-d_6): δ1.33 ppm (t, 3H, CH_3), 3.26 (s, 2H, NH, D_2O exchangeable), 4.36 (q, 2H, CH_2), 8.08 (s, 2H, NH_2, D_2O exchangeable), 8.44 (s, 1H, pyrazole H-7); mass spectrum at m/z 251 (100%).

##^{1}H-NMR (DMSO-d_6): δ1.25 ppm (t, 3H, CH_3), 1.38 (t, 3H, CH_3), 4.22-4.35 (m, 4H, $2CH_2$), 7.35 (s, 2H, NH_2, D_2O exchangeable) and 7.89 (s, 1H, pyrazole H-); mass spectrum at m/z 280 (47.0%).

###^{1}H-NMR (DMSO-d_6): δ1.35 ppm (t, 3H, CH_3), 4.30(q, 2H, CH_2), 6.33 (s, 2H, NH_2, D_2O exchangeable) and 7.60-8.22 (m, 6H, 5 aromatic protons+pyrazole H-).

Required: C, 48.72; H, 5.62; N, 21.30% .

Found: C, 48.8; H, 5.6; N, 21.2% .

Ethyl 3-(N-chloroacetylamino)-2H-pyrazole-4-carboxylate 11b: A mixture of 1 (0.005 mol) and an equimolecular amount of chloroacetyl chloride in anhydrous dioxane (15 ml) were heated under reflux for 3 hours. The reaction mixture was cooled and then neutralized by adding a solution of sodium acetate (PH~6). The solid so formed was filtered off, washed with water, dried and crystallized from dilute dioxane to yield 0.83 g (72.17%) of 11b; m.p. 213°C; IR: 3319 cm^{-1} (NH), 3220 (NH), 1699 (CO) and 1685 (CO). ^{1}H-NMR (DMSO-d_6): δ 1.26 ppm (t, 3H, CH_3), 4.21-4.32 (m, 4H, $2CH_2$), 8.09 (s, 1H, pyrazole H-5), 10.24 (s, 1H, NH, D_2O exchangeable) and 10.35 (s, 1H, NH, D_2O exchangeable); mass spectrum at m/z 231 (39.4%).

Analysis: $C_8H_{10}ClN_3O_3$ (231.636)

Required: C, 41.48; H, 4.35; Cl, 15.3; N, 18.14% .

Found: C, 41.5; H, 4.4; Cl, 15.3; N, 18.1% .

Ethyl 5-aryl-6-cyano-7-oxo-4H,7H-pyrazolo[1,5-a]pyrimidine-3-car-boxylates (13a,b)

A mixture 0.005 mol of 1 and some α-cyanocinnamates 6a,b was heated in pyridine under reflux for 24 hours.

The reaction mixture was cooled and acidified with dilute hydrochloric acid, whereby, the solid that precipitated was filtered off, dried and crystallized from dilute dioxane.

Ethyl 6-cyano-7-oxo-5-phenyl-4H,7H-pyrazolo[1,5-a]pyrimidine-3-carboxylate 13a: Yield, 1.08 g (70.58%), m.p. 250°C; IR: 3425 cm^{-1} (NH_2), 2237 (CN) and 1718-1689 (2CO).

Analysis: $C_{16}H_{12}N_4O_3$ (308.29)

Required: C, 62.33; H, 3.92; N, 18.17%

Found: C, 62.4; H, 4.0; N, 18.1%

Ethyl 5-[4-chlorophenyl-6-cyano-7-oxo-4H,7H-pyrazolo[1,5-a]pyri-midine-3-carboxylate 13b: Yield, 1.34 g (78.45%), m.p. 322°C; IR: 3317 cm^{-1} (NH), 2230 (CN) and 1725-1686 (2CO); mass spectrum at m/z 342 (100.0%) and 344 (34.2%).

Analysis: $C_{16}H_{11}ClN_4O_3$ (342.73)

Required: C, 56.07; H, 3.23; Cl, 10.34; N, 16.36%

Found: C, 56.1; H, 3.3; Cl, 10.4; N, 16.3%

REFERENCES

1. Tseng, C. P. *U.S. Pat.* 1989, 4838925; *Chem. Abstr.* **1990**, *112*, 7508.
2. Sakane, K.; Kawabata, K.; Inamoto, Y. *Eur. Pat.* 1989, 332156; *Chem. Abstr.* **1990**, *112*, 216538.
3. Fujikawa, Y.; Suzuki, M.; Sakashita, M.; Tanaka, S.; Wakamatsu, M.; Miyasaka, S. *Tokyo Jp.* 1989, 1221381; *Chem. Abstr.* **1990**, *112*, 158268.
4. Tseng, S. S.; Brabander, J. H.; Epstein, W. J. *U.S. Pat.* 1990, 4963553; *Chem. Abstr.* **1991**, *114*, 228937.
5. Taylor, R. C.; Stauffer, F. H.; Tomezuk, B. E. *U.S. Pat.* 1992, 5114944; *Chem. Abstr.* **1992**, *117*, 90318.
6. Hibino, H.; Myamoto, Y.; Myajima, M.; Maeda, H. *Tokyo Jp.* 1993, 5213756; *Chem. Abstr.* **1993**, *119*, 256547.
7. Allen, E. E.; Maccoss, M.; Chakravarty, P. K.; Patchett, A. A.; Greenlee, W. J.; Walsh, T. F. *Eur. Pat.* 1992, 490587; *Chem. Abstr.* **1992**, *117*, 151008.
8. Gatta, F.; Perotti, F.; Gradoni, L.; Gramiccia, M.; Orsini, S.; Palazzo, G.; Rossi, V. *Eur. J. Med. Chem.* **1990**, *25*, 419.
9. Schmidt, P.; Druey, J. *Helvetica Chemica Acta* **1956**, *29*, 986.
10. Hussain, S. M.; El-Reedy, A. M.; El-Sharabasy, S. A. *Tetrahedron* **1988**, *44*, 241.