Reactivity of Cinnamonitriles with 2-Cyano- and 2-Ethoxycarbonylacetohydrazides: A Novel One-step Preparation and Crystal Structure of 3-Oxopyrazolo[3,4-*b*]pyridines

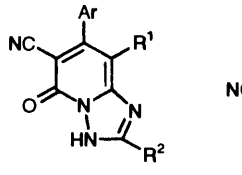
Ali Hadi,[a] Nazario Martin,[a] Carmen Méndez,[a] Margarita Quinteiro,[a] Carlos Seoane,[a] José L. Soto,[a] Armando Albert[b] and Félix H. Cano[b]

[a] *Departamento de Química Orgánica, Facultad de Química, Universidad Complutense, 28040-Madrid, Spain*

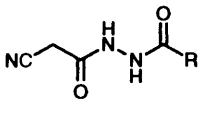
[b] *U.E.I. Cristalografía, Instituto Rocasolano, CSIC, Serrano 119, 28040-Madrid, Spain*

A novel one-step synthesis of pyrazolo[3,4-*b*]pyridines **8** from α-benzoylcinnamonitriles and 2'-acetyl-2-cyanoacetohydrazide **2** is described. The X-ray crystallographic analysis revealed the presence of the enol tautomer and the existence of a strong network of hydrogen bonds. The use of 2-ethoxycarbonylacetohydrazide derivatives **12** as starting materials led only to the intermediate dihydro-2-pyridones **13**. 2-Cyanoacetohydrazide **11** led to the novel triazolo[1,5-*a*]pyridinones **15**.

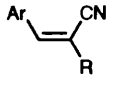
We have previously described a very convenient, one-step method for the synthesis of [1,2,4]triazolo[1,5-*a*]pyridines **1** by reaction of *N*-substituted 2-cyanoacetohydrazides **2** with 2-cyanocinnamonitriles **3**.[1] The experimental procedure that leads to **1** as the piperidinium salt, from which compound **1** was liberated by neutralization, proved to be of general application. Interestingly, substituting the alkoxycarbonyl group for the cyano group in the 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 that upon neutralization gave the neutral pyrazolo[3,4-*b*]pyridinones **4**.[2]



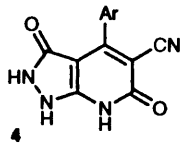
1 a R^1 = CN, R^2 = Me
b R^1 = CN, R^2 = Ph
c R^1 = CO_2R, R^2 = CH_2Ph



2 a R = Me
b R = Ph
c R = CH_2Ph



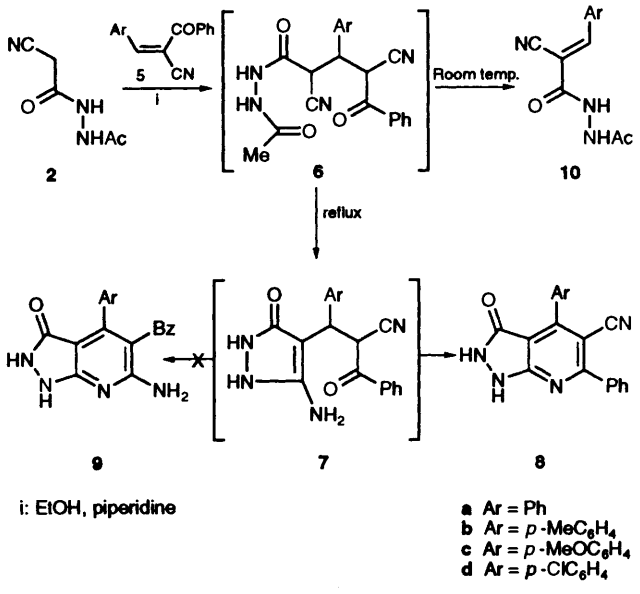
3 a = CN
b = CO_2R



4

Taking into account the effect of the substituents on the course of the cyclization, we have investigated the reaction of 2-benzoylcinnamonitriles **5** with *N*-acyl-2-cyanoacetohydrazide **2**. In this paper we report these results, from which novel pyrazolo[3,4-*b*]pyridines **8** resulted. The absence now of a carbonyl group in the pyridine ring, in comparison with **1**, is responsible for the direct formation of the neutral molecule. To the best of our knowledge, this is the first one-pot reaction for the synthesis of these neutral heterocyclic systems.[3] On the other hand, we have prepared 2'-benzoyl-2-ethoxycarbonylacetohydrazide **12** and carried out the reaction with 2-cyanocinnamonitriles **3a** and 2-alkoxycarbonylcinnamonitriles **3b**. Finally, the reaction of 2-cyanoacetohydrazide **2a** with 2-alkoxycarbonylcinnamonitrile **3b** led to the 1,6-diamino-2-pyridone **14**[4] which reacted with acetic anhydride to yield the corresponding substituted [1,2,4]triazolo[1,5-*a*]pyridinone **15**.

Formation of pyrazolo[3,4-*b*]pyridine **8** can be rationalized as depicted in Scheme 1. The Michael addition of the anion of the 2'-acetyl-2-cyanoacetohydrazide **2**, generated in the basic



i: EtOH, piperidine

a Ar = Ph
b Ar = *p*-MeC_6H_4
c Ar = *p*-$MeOC_6H_4$
d Ar = *p*-ClC_6H_4

Scheme 1

medium, to the 2-benzoylcinnamonitriles **5** leads to the adducts **6**. Nucleophilic attack by a nitrogen at the cyano group through a 5-*exo-dig* cyclization[5] forms the aminopyrazole intermediate **7** which undergoes a subsequent regioselective 6-*exo-trig* cyclization followed by dehydration and spontaneous aromatization to the novel pyrazolo[3,4-*b*]pyridine **8**. Compounds **8** were thus obtained as stable white solids with high melting points in moderate yields (see Experimental section).

It is worth mentioning that the alternative 6-*exo-dig* cyclization in **7**, leading to the pyrazolo[3,4-*b*]pyridine **9** was not observed. This result is in contrast with the previously reported synthesis of 1,6-diamino-2-pyridones[6] in which the cyclizations by the cyano or carbonyl groups were temperature controlled. Here, pyrazolo[3,4-*b*]pyridine **8** was obtained at reflux temperature as the only reaction product. At room temperature, formation of a complex mixture was observed from which only compound **10**, resulting from the retro-Michael reaction of the intermediate **6**, could be identified.

Compounds **8** were obtained as the neutral pyrazolo[3,4-*b*]pyridine system. These compounds showed, in addition to the cyano band that appears at 2220 cm^{-1}, a characteristic broad band at 2500–3300 cm^{-1} in their IR spectra. The H^1 NMR spectra showed the NH group as a small broad singlet at 11.2–

Table 1 Geometrical characteristics of compound **8a**

(a) Bond distances (Å)

N(1)–C(2)	1.341(5)	C(11)–C(16)	1.387(5)
N(1)–C(9)	1.329(4)	C(12)–C(13)	1.387(6)
C(2)–N(3)	1.339(4)	C(13)–C(14)	1.376(8)
C(2)–C(6)	1.395(4)	C(14)–C(15)	1.359(8)
N(3)–N(4)	1.380(4)	C(15)–C(16)	1.380(6)
N(4)–C(5)	1.308(4)	C(17)–N(18)	1.144(5)
C(5)–C(6)	1.439(5)	C(19)–C(20)	1.381(6)
C(5)–O(10)	1.326(4)	C(19)–C(24)	1.393(5)
C(6)–C(7)	1.401(4)	C(20)–C(21)	1.387(7)
C(7)–C(8)	1.407(5)	C(21)–C(22)	1.370(6)
C(7)–C(11)	1.477(4)	C(22)–C(23)	1.371(7)
C(8)–C(9)	1.420(4)	C(23)–C(24)	1.387(7)
C(8)–C(17)	1.437(4)	N(25)–C(26)	1.141(7)
C(9)–C(19)	1.494(5)	C(26)–C(27)	1.418(7)
C(11)–C(12)	1.392(5)		

(b) Bond angles (°)

C(2)–N(1)–C(9)	115.0(3)	N(1)–C(9)–C(19)	113.8(3)
N(1)–C(2)–C(6)	127.2(3)	C(7)–C(11)–C(16)	121.6(3)
N(1)–C(2)–N(3)	124.3(3)	C(7)–C(11)–C(12)	119.1(3)
N(3)–C(2)–C(6)	108.5(3)	C(12)–C(11)–C(16)	119.3(3)
C(2)–N(3)–N(4)	110.4(2)	C(11)–C(12)–C(13)	119.5(4)
N(3)–N(4)–N(5)	106.8(3)	C(12)–C(13)–C(14)	120.1(4)
N(4)–C(5)–O(10)	122.6(3)	C(13)–C(14)–C(15)	120.9(4)
N(4)–C(5)–C(6)	110.9(3)	C(14)–C(15)–C(16)	119.9(5)
C(6)–C(5)–O(10)	126.6(3)	C(11)–C(16)–C(15)	120.5(4)
C(2)–C(6)–C(5)	103.4(3)	C(8)–C(17)–N(18)	179.1(4)
C(5)–C(6)–C(7)	138.0(3)	C(9)–C(19)–C(24)	123.1(3)
C(2)–C(6)–C(7)	118.6(3)	C(9)–C(19)–C(20)	118.0(3)
C(6)–C(7)–C(11)	123.2(3)	C(20)–C(19)–C(24)	118.9(3)
C(6)–C(7)–C(8)	114.7(3)	C(19)–C(20)–C(21)	121.0(3)
C(8)–C(7)–C(11)	122.0(3)	C(20)–C(21)–C(22)	119.7(4)
C(7)–C(8)–C(17)	118.0(3)	C(21)–C(22)–C(23)	120.1(4)
C(7)–C(8)–C(9)	122.1(3)	C(22)–C(23)–C(24)	120.9(4)
C(9)–C(8)–C(17)	119.6(3)	C(19)–C(24)–C(23)	119.5(3)
N(1)–C(9)–C(8)	122.4(3)	N(25)–C(26)–C(27)	179.1(7)
C(8)–C(9)–C(19)	123.7(3)		

11.4 ppm. According to the molecular weight several isomeric structures could be drawn and, consequently, the pyrazolo[3,4-*b*]pyridine structure was unambiguously determined by X-ray crystallographic analysis. Scarce crystallographical data were found in the literature on this fused system.[7] The geometrical features of compound **8a** are listed in Table 1. A perspective drawing of **8a** with the atomic labelling used in the crystallographic study is presented in Fig. 1. The bond distances and angles of compound **8a** reveal a delocalization of the π-electrons of the fused system, which exhibit a somewhat distorted planarity. The pyridine ring showed a boat conformation with C-2 and C-8 out-of-the-plane and the pyrazole ring in an envelope conformation with the N-3 atom. The phenyl rings are not orthogonal to the fused heterocyclic system, forming 54.5(1)° and 40.3(1)° respectively (see Fig. 1).

It is worth noting that, in the solid state, compound **8a** appears as the enolic tautomer. This result is in agreement with the previously described one for the related pyrazolo[4,3-*c*]pyridines which exist in the hydroxy form.[8] The majority of reports[3] on 1- and 2-substituted 3-hydroxypyrazolopyridines, however, quote IR absorptions attributed to ν(CO). The crystal packing showed the presence of hydrogen bonds and aromatic interactions. Thus, each molecule is strongly linked by hydrogen bonds to a molecule of solvent (MeCN) and to another heterocyclic molecule forming dimers [N(3)–H(3)···N(25), 2.93(1) Å, 174(4)°, x, $y+1$, z and O(10)–H(10)···N(4), 2.721(4) Å, 174(4)°, $1-x$, $1-y$, $-z$; Donor-H···Acceptor, Distance D···A, Angle D-H···A).

There is also a complex system of aromatic interactions, involving all the rings of the molecule, and showing both a

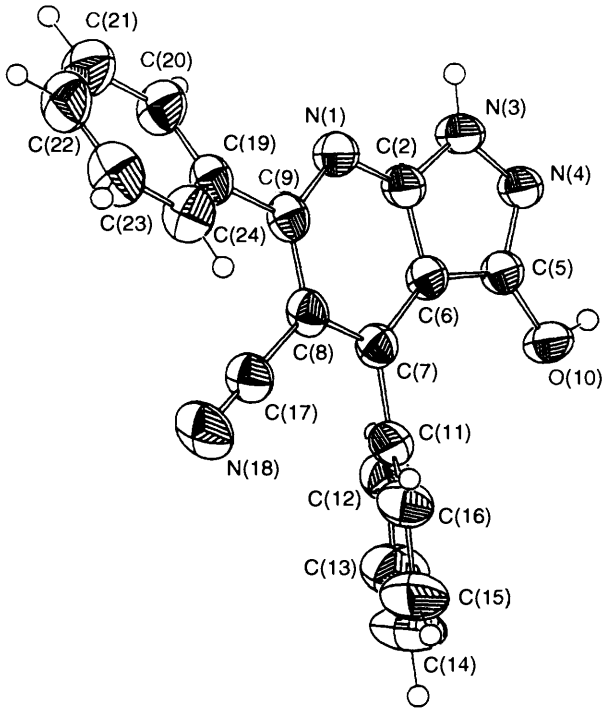


Fig. 1 Molecular structure of compound **8a** showing the atomic numbering.[21] The solvent molecule is not shown.

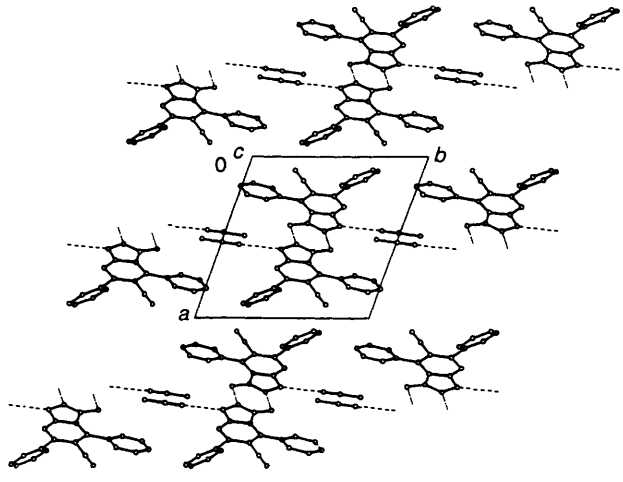
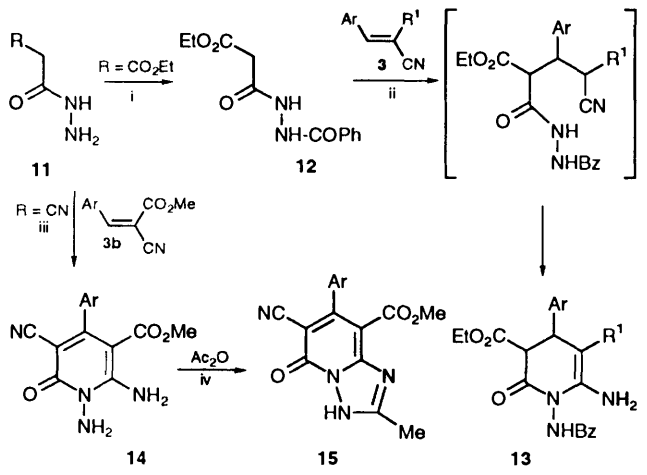


Fig. 2 Crystal packing of compound **8a**, as projected along the c axis,[22] showing the intramolecular interactions.

stacking pattern and a herringbone motif in the three directions of the crystal[9,10] (see Fig. 2).

Taking into account the required presence of the cyano group of the cyanoacetohydrazide in the intermediate **6** to form the pyrazolo[3,4-*b*]pyridine **8**, we carried out (Scheme 2) the reaction of 2′-benzoyl-2-ethoxycarbonylacetohydrazide **12** with 2-cyanocinnamonitrile **3** to explore the possible alternative regioselective cyclizations. However, as a simpler case, we used cinnamonitrile bearing a second cyano group **3a** (R=CN). Compound **12** could be obtained by careful acylation of ethoxycarbonylacetohydrazide[11] **11** with benzoyl chloride at 0 °C. Reaction of 2′-benzoyl-2-ethoxycarbonylacetohydrazide **12** with 2-cyanocinnamonitrile **3a** in alcoholic solution at room temperature and in the presence of piperidine led, in all cases, to the corresponding *N*-substituted 3,4-dihydro-2-pyridones **13** as the only isolated product in good yields. The reaction of **12** with 2-alkoxycarbonylcinnamonitriles **3b** yielded, in a similar way,



13 a Ar = Ph, R^1 = CN
b Ar = *p*-MeC_6H_4, R^1 = CN
c Ar = *p*-$MeOC_6H_4$, R^1 = CN
d Ar = *p*-ClC_6H_4, R^1 = CN
e Ar = *p*-$O_2NC_6H_4$, R^1 = CN
f Ar = Ph, R^1 = CO_2Me
g Ar = *p*-MeC_6H_4, R^1 = CO_2Me
h Ar = *p*-$MeOC_6H_4$, R^1 = CO_2Me
i Ar = *p*-ClC_6H_4, R^1 = CO_2Me
j Ar = *p*-$O_2NC_6H_4$, R^1 = CO_2Me
k Ar = Ph, R^1 = CO_2Et
l Ar = *p*-MeC_6H_4, R^1 = CO_2Et
m Ar = *p*-$MeOC_6H_4$, R^1 = CO_2Et
n Ar = *p*-ClC_6H_4, R^1 = CO_2Et
o Ar = *p*-$O_2NC_6H_4$, R^1 = CO_2Et

15 a Ar = Ph
b Ar = *p*-MeC_6H_4
c Ar = *p*-$MeOC_6H_4$
d Ar = *p*-ClC_6H_4
e Ar = *p*-$O_2NC_6H_4$

Scheme 2 *Reagents and conditions:* i, BzCl, 0 °C, K_2CO_3; ii, EtOH–piperidine, room temp. or reflux; iii, dry MeOH-piperidine, room temp.; iv, reflux

the corresponding 5-alkoxycarbonyl-3,4-dihydro-2-pyridones **13**.

Formation of **13** could be accounted for by conjugate addition of the carbanion of **12** to the substituted cinnamonitrile, followed by regioselective 6-*exo-dig* cyclization to the pyridine ring. Attempts to form the triazolo[1,5-*a*]pyridine[1] from **13** by carrying out the reaction at reflux temperature led only to compound **13** in a slightly improved yield.

The influence of the electron-withdrawing substituent in position 2 of the acetohydrazide could also be observed in the reaction of 2-cyanoacetohydrazide **11b** with 2-methoxycarbonylcinnamonitriles **3b**, which yielded the corresponding aromatic 1,6-diamino-2-pyridones **14** which were isolated in moderate yields. Treatment of **14** with acetic anhydride at reflux temperature led to the novel triazolo[1,5-*a*]pyridinones **15** in good yields (Scheme 2). The use of catalytic amounts of piperidine gave under these reaction conditions, compounds **15** as stable neutral solids.

In conclusion, we have developed a novel, one-step procedure to prepare pyrazolo[3,4-*b*]pyridines from alicyclic starting compounds by modification of a recently described procedure for synthesizing triazolo[1,5-*a*]pyridinones.[1] We have studied the molecular structure of these 3-oxopyrazolo[3,4-*b*]pyridines by X-ray crystallography and confirmed the presence, in the solid state, of the more favoured enol tautomer. Additionally, we have evaluated the use of *N*-acyl-2-ethoxycarbonylacetohydrazide for the preparation of these fused heterocyclic systems. Finally, a novel series of triazolo[1,5-*a*]pyridinones **15** have been obtained from 2-cyanoacetohydrazide in a two-step procedure.

Experimental

M.p.s were determined in capillary tubes in a GallenKamp instrument and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz on a Varian VXR 300S spectrometer. All NMR spectra were recorded for $(CD_3)_2SO$ solutions, chemical shifts being given as δ values with respect to $SiMe_4$ as the internal standard. IR spectra were measured with a Perkin-Elmer 781 instrument for KBr pellets. Mass spectra were obtained with a Varian MAT 711 machine. Microanalyses were performed by the Universidad Complutense Microanalytical Service. The reactions were monitored by TLC performed on silica gel plates (Merck-60F) and using chloroform–methanol (1 : 1) or toluene–ethyl acetate (1 : 1) as the eluent.

Cyanoacetohydrazide, malononitrile, ethyl cyanoacetate, methyl cyanoacetate 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 (Aldrich), but the remaining arylidenemalononitriles and arylidenecyanoacetates were prepared from aromatic aldehydes by following standard procedures.[12]

4-Aryl-5-cyano-6-phenylpyrazolo[3,4-b]*pyridin*-3(2H)-*one* **8**: *General Procedure.*—To a suspension of 2'-acetyl-2-cyanoacetohydrazide (0.5 g, 3.55 mmol) and the corresponding 2-benzoylcinnamonitrile (3.55 mmol) in dry ethanol (5 cm^3), a few drops of piperidine were added. The reaction mixture was refluxed for a variable length of time (24–36 h) until the starting material was exhausted and a solid had been precipitated. It was filtered off and recrystallized from the appropriate solvent.

5-Cyano-4,6-diphenylpyrazolo[3,4-b]*pyridin*-3(2H)-*one* **8a**. This compound was obtained after 24 h in 35% yield, m.p. 293–294 °C (from MeCN) (Found: C, 72.7; H, 3.8; N, 17.75. $C_{19}H_{12}N_4O$ requires C, 73.0; H, 3.85; N, 17.95); ν_{max} 3200–2500, 2220, 1590, 1550, 1500, 1200 and 700 cm^{-1}; δ_H 7.56 (6 H, m, ArH), 7.68 (2 H, m, ArH), 7.86 (2 H, d, ArH) and 11.29 (1 H, s, NH); δ_C 98.31, 100.99 (C-3a, -5), 118.49 (CN), 128.03 (2 C), 128.43 (2 C), 129.43 (2 C), 129.95 (2 C), 130.32, 132.14, 133.39, 138.31 (ArH), 151.71, 153.41, 154.97 (C-4, -6, -7a) and 161.07 (CO); *m/z* (relative intensity): 312 (M^+, 80), 311 (100) and 255 (10).

Crystal data for compound **8a**: $C_{19}H_{12}N_3O$·MeCN, M_w = 339.376, triclinic, $P\bar{1}$, a = 12.181(1) Å, b = 11.761(2) Å, c = 7.0312(3) Å, α = 90.52(1)°, β = 104.63(1)°, ν = 108.81(1)°, V = 918.1(2) $Å^3$, Z = 2, D_c = 1.23 g cm^{-3}, $F(000)$ = 354, μ = 5.96 cm^{-1}. Refined cell parameters were obtained from setting angles of 62 reflections. A prismatic colourless crystal (0.40 × 0.12 × 0.10 mm) was used for the diffractometric analysis.

Data collection: Automatic four-circle diffractometer Philips PW 1100 with graphite orientated monochromated Cu-Kα radiation. The intensity data were collected using the $\omega/2\theta$ scan mode between $2 < \theta > 65°$; two standard reflections were measured every 90 min with no intensity variation. A total of 3121 reflections were measured and 2196 were considered as observed [$I > 3\sigma(I)$ criterium]. The data were corrected for Lorentz and polarization effects.

Structure solution and refinement: The structure was solved by direct methods using SIR88[13] and DIRDIF92[14] and successive Fourier syntheses. The H atom of the OH group was located from Fourier difference. The remaining H atoms were calculated, except those involved in the solvent molecule; all of them were included in a mixed refinement. A convenient weighting scheme was applied to obtain flat dependence in $\langle w\Delta^2F\rangle$ *vs.* $\langle F_0\rangle$ and $\langle \sin\theta/\lambda\rangle$.[15] The final R (RW) value was 5.9 (6.5). Atomic scattering factors for the compound were taken from International Tables for X-ray Crystallography[16] and calculations were performed using XRAY80,[17] XTAL,[18] HSEARCH[19] and PARST.[20]

5-*Cyano*-4-(p-*tolyl*)-3-*oxo*-6-*phenylpyrazolo*[3,4-b]*pyridine* **8b**. This compound was obtained after 36 h in 19% yield, m.p. 300–302 °C (MeCN) (Found: C, 73.3; H, 4.25; N, 17.2. $C_{20}H_{14}N_4O$ requires C, 73.6; H, 4.3; N, 17.2); ν_{max}/cm ^{1} 3200–2500, 2220, 1590, 1550, 1500, 1200 and 700; δ_H 2.42 (3 H, s, CH_3), 7.36 (2 H, d, ArH), 7.56 (5 H, m, ArH), 7.85 (2 H, d, ArH) and 11.2 (1 H, s, NH).

5-*Cyano*-4-(p-*methoxyphenyl*)-3-*oxo*-6-*phenylpyrazolo*[3,4-b]*pyridine* **8c**. This compound was obtained after 24 h in 41% yield, m.p. 324–325 °C (MeCN) (Found: C, 69.75; H, 4.1; N, 16.15. $C_{20}H_{14}N_4O_2$ requires C, 70.15; H, 4.1; N, 16.35); ν_{max}/cm^{-1} 3300–2500, 2220, 1600, 1560, 1510, 1200 and 700 cm^{-1}; δ_H 3.87 (3 H, s, OMe), 7.11 (2 H, d, ArH), 7.59 (3 H, m, ArH), 7.68 (2 H, d, ArH) and 7.87 (2 H, m, ArH).

4-(p-*Chlorophenyl*)-5-*cyano*-3-*oxo*-6-*phenylpyrazolo*[3,4-b]-*pyridine* **8d**. This compound was obtained after 36 h in 29% yield, m.p. 312–314 °C (MeCN) (Found: C, 65.4; H, 3.1; Cl, 10.55; N, 16.15. $C_{19}H_{11}ClN_4O$ requires C, 65.8; H, 3.15; Cl, 10.25; N, 16.15) ν_{max}/cm^{-1} 3200–2500, 2220, 1590, 1550, 1500, 1200 and 700; δ_H 7.63 (5 H, m, ArH), 7.73 (2 H, d, ArH), 7.78 (2 H, d, ArH) and 11.4 (1 H, s, NH); δ_C 98.53, 101.02 (C-3a, -5), 118.25 (CN), 128.14 (2 C), 128.4 (2 C), 129.36 (2 C), 129.95, 131.86 (2 C), 132.18, 134.93, 138.19 (ArH), 150.77, 151.7, 154.86 (C 4, -6, -7a) and 161.03 (CO).

2′-*Benzoyl*-2-*ethoxycarbonylacetohydrazide* **12**.—To a stirred solution of 2-ethoxycarbonylacetohydrazide **10** (2.7 g, 18.8 mmol) in water (3 cm^3) at 0 °C, were added benzoyl chloride (4.3 g, 28.2 mmol) from a dropping funnel and a solution of potassium carbonate (1.29 g) in water (1.5 cm^3). After 10 min a precipitate formed and this was filtered off, washed with water and recrystallized from ethanol to yield white crystals (66%), m.p. 128–130 °C (Found: C, 57.75; H, 5.7; N, 11.35. $C_{12}H_{14}N_2O_4$ requires C, 57.6; H, 5.6; N, 11.2); ν_{max}/cm^{-1} 3300 (NH), 1760 (CO_2), 1670 (CO), 1600, 1520, 1500, 1420, 1380, 1300, 1240, 1160 and 1000; δ_H 1.21 (3 H, t, Me), 3.36 (2 H, s, CH_2), 4.11 (2 H, q, CH_2O), 7.4–7.6 (3 H, m, ArH), 7.87 (2 H, d, ArH) and 10.19 and 10.49 (2 H, br, 2 × NH); δ_C 14.25 (Me), 40.87 (CH_2), 60.87 (CH_2O), 127.68 (2 C), 128.67 (2 C), 132.09 (ArH), 132.47 (*ipso* ArH), 164.71, 165.49 (2 CO) and 167.46 (CO_2).

5-*Substituted* 6-*Amino*-4-*aryl*-1-*benzoylamido*-3,4-*dihydro*-2(1H)-*pyridones* **13**: *General Procedure*.—To a solution of 2′-benzoyl-2-ethoxycarbonylacetohydrazide **12** (0.5 g, 2 mmol) and the corresponding 2-substituted cinnamonitrile **3** (2 mmol) in dry ethanol (15 cm^3), piperidine (3–4 drops) was added. The reaction mixture, stirred either at room temperature (10–25 h) or at reflux temperature (5–10 h), precipitated a solid. This was filtered off and recrystallized from the appropriate solvent.

6-*Amino*-1-*benzamido*-5-*cyano*-3-*ethoxycarbonyl*-4-*phenyl*-3,4-*dihydro*-2(1H)-*pyridone* **13a**. This compound was obtained after 20 h of stirring in 56% yield, m.p. 196–198 °C (MeCN–H_2O) (Found: C, 65.55; H, 4.8; N, 14.05. $C_{22}H_{20}N_4O_4$ requires C, 65.35; H, 4.95; N, 13.85%); ν_{max}/cm^{-1} 3400, 3310, 3200, 2990, 2200, 1750, 1730, 1700, 1650, 1600, 1530, 1440, 1350, 1160 and 710; δ_H(diastereoisomeric mixture; major isomer) 1.07 (3 H, t, Me), 3.8–4.2 (4 H, m, CH_2O, 2 CH), 6.85–6.92 (5 H, m, ArH), 7.28–7.62 (5 H, m, ArH), 8.0 (2 H, d, NH_2) and 10.87–10.98 (1 H, br s, NH); *m*/*z* (relative intensity) 404 (M^+, 5), 331 (5), 284 (45), 240 (20), 212 (72), 203 (24), 163 (55), 154 (100) and 127 (100).

6-*Amino*-1-*benzamido*-5-*cyano*-3-*ethoxycarbonyl*-4-(p-*tolyl*)-3,4-*dihydro*-2(1H)*pyridone* **13b**. This compound was obtained after 19 h of stirring in 47% yield, m.p. 184–186 °C (MeCN–H_2O) (Found: C, 66.1; H, 5.1; N, 13.45. $C_{23}H_{22}N_4O_4$ requires C, 66.05; H, 5.25; N, 13.40); ν_{max}/cm^{-1} 3400, 3310, 3200, 2990, 2200, 1750, 1730, 1700, 1650, 1600, 1530, 1440, 1350, 1160 and 710; δ_H(diastereoisomeric mixture; major isomer) 1.1–1.2 (3 H, t, Me), 2.39 (3 H, s, Me), 3.8–4.2 (4 H, m, CH_2O, 2 CH), 6.85 (2 H, d, ArH), 7.14–7.64 (7 H, m, ArH), 8.0 (2 H, d, NH_2) and 10.4 (1 H, br s, NH).

6-*Amino*-1-*benzamido*-5-*cyano*-3-*ethoxycarbonyl*-4-(p-*methoxyphenyl*)-2-*oxo*-3,4-*dihydro*-2(1H)-*pyridone* **13c**. This compound was obtained after 18 h of stirring in 56% yield, m.p. 144–146 °C (MeCN–H_2O) (Found: C, 63.6; H, 4.85; N, 12.9. $C_{23}H_{22}N_4O_5$ requires C, 63.6; H, 5.05; N, 12.9); ν_{max}/cm ^{1} 3400, 3310, 3200, 2990, 2200, 1750, 1730, 1700, 1650, 1600, 1530, 1440, 1350, 1160 and 710; δ_H(diastereoisomeric mixture; major isomer) 1.12 (3 H, t, Me), 3.62 (3 H, s, OMe), 3.74 (1 H, d, CH), 3.8–4.0 (3 H, m, CH_2O, CH), 6.68–6.8 (4 H, m, ArH), 7.15–7.55 (5 H, m, ArH), 7.9 (2 H, d, NH_2) and 10.82 (1 H, br s, NH).

6-*Amino*-1-*benzamido*-4-(p-*chlorophenyl*)-5-*cyano*-3-*ethoxycarbonyl*-3,4-*dihydro*-2(1H)-*pyridone* **13d**. This compound was obtained after 16 h of stirring in 61% yield, m.p. 216–218 °C (MeCN–H_2O) (Found: C, 60.3; H, 4.3; N, 13.0. $C_{22}H_{19}ClN_4O_4$ requires C, 60.2; H, 4.35; N, 12.75); ν_{max}/cm^{-1} 3400, 3310, 3200, 2980, 2200, 1750, 1730, 1700, 1650, 1600, 1530, 1440, 1350, 1160 and 710; δ_H(diastereoisomeric mixture; major isomer) 1.13 (3 H, t, Me), 3.9–4.3 (4 H, m, CH_2O, 2 CH), 7.0 (2 H, d, ArH), 7.4 (3 H, m, ArH), 7.48–7.68 (4 H, m, ArH), 8.0 (2 H, d, NH_2) and 10.9 (1 H, br s, NH).

6-*Amino*-1-*benzamido*-5-*cyano*-3-*ethoxycarbonyl*-4-(p-*nitrophenyl*-3,4-*dihydro*-2(1H)-*pyridone* **13e**. This compound was obtained after 18 h of stirring in 50% yield, m.p. 230–232 °C (MeCN–H_2O) (Found: C, 58.9; H, 4.1; N, 15.65. $C_{22}H_{19}N_5O_6$ requires C, 58.8; H, 4.25; N, 15.6); ν_{max}/cm^{-1} 3400, 3310, 3200, 2980, 2200, 1750, 1730, 1700, 1650, 1600, 1530, 1440, 1350, 1160 and 710; δ_H(diastereoisomeric mixture; major isomer) 1.16 (3 H, t, Me), 4.13 (2 H, q, CH_2O), 4.32 (1 H, d, CH), 4.38 (1 H, d, CH), 7.06 (2 H, d, ArH), 7.53–8.0 (7 H, m, ArH), 8.22 (2 H, d, NH_2) and 10.9 (1 H, br s, NH); *m*/*z* (relative intensity) 449 (M^+, 10), 431 (4), 376 (4), 359 (10), 329 (80), 285 (20), 257 (90), 250 (84), 232 (24), 169 (6), 153 (100), 105 (100), 77 (100) and 45 (100).

6-*Amino*-1-*benzamido*-3-*ethoxycarbonyl*-5-*methoxycarbonyl*-4-*phenyl*-3,4-*dihydro*-2-(1H)-*pyridone* **13f**. This compound was obtained after 25 h of stirring in 61% yield, m.p. 171–173 °C (toluene or methanol) (Found: C, 63.35; H, 5.3; N, 9.6. $C_{23}H_{23}N_3O_6$ requires C, 63.15; H, 5.25; N, 9.6); ν_{max}/cm^{-1} 3400, 3310, 3260, 2980, 1740, 1710, 1670, 1610, 1520, 1470, 1440, 1370, 1320, 1270, 1250, 1170, 770 and 700; δ_H(diastereoisomeric mixture; major isomer) 1.2 (3 H, t, Me), 3.5 (3 H, s, OMe), 3.8 (1 H, d, CH), 4.2 (2 H, m, CH_2O), 4.6 (1 H, d, CH), 7.2–7.4 (5 H, m, ArH), 7.5–7.63 (5 H, m, ArH), 8.45 (2 H, d, NH_2) and 11.0 (1 H, br s, NH).

6-*Amino*-1-*benzamido*-3-*ethoxycarbonyl*-5-*methoxycarbonyl*-4-(p-*tolyl*)-3,4-*dihydro*-2(1H)-*pyridone* **13g**. This compound was obtained after 20 h of stirring in 88% yield, m.p. 202–204 °C (methanol) (Found: C, 63.7; H, 5.65; N, 9.4. $C_{24}H_{25}N_3O_6$ requires C, 63.85; H, 5.55; N, 9.3); ν_{max}/cm^{-1} 3400, 3300, 2980, 1740, 1710, 1670, 1610, 1520, 1470, 1440, 1370, 1320, 1270, 1250, 1170, 800 and 720; δ_H(diastereoisomeric mixture; major isomer) 1.2 (3 H, t, Me), 2.27 (3 H, s, Me), 3.5 (3 H, s, OMe), 3.73 (1 H, d, CH), 4.19 (2 H, q, CH_2O), 4.5 (1 H, d, CH), 7.09–7.13 (3 H, m, ArH), 7.41–7.43 (2 H, d, ArH), 7.52–7.64 (4 H, m, ArH), 8.05 (2 H, d, NH_2) and 10.8–11.11 (1 H, br s, NH).

6-*Amino*-1-*benzamido*-3-*ethoxycarbonyl*-5-*methoxycarbonyl*-4-(p-*methoxyphenyl*)-3,4-*dihydro*-2(1H)-*pyridone* **13h**. This compound was obtained after 23 h of stirring in 75% yield, m.p. 193–195 °C (toluene) (Found: C, 61.6; H, 5.4; N, 9.15. $C_{24}H_{25}N_3O_7$ requires C, 61.65; H, 5.35; N, 9.0); ν_{max}/cm^{-1} 3400, 3260, 2960, 1740, 1710, 1670, 1610, 1520, 1470, 1440, 1320, 1250, 1200, 1180, 800 and 720; δ_H(diastereoisomeric mixture; major isomer) 1.17 (3 H, t, Me), 3.5 (3 H, s, OMe), 3.73 (4 H, br s, OMe, CH), 4.18 (2 H, m, CH_2O), 4.48 (1 H, d, CH), 6.8–6.85 (3 H, m,

ArH), 7.43–7.66 (6 H, m, ArH), 8.08 (2 H, d, NH_2) and 10.8 (1 H, br s, NH).

6-*Amino*-1-*benzamido*-4-(p-*chlorophenyl*)-3-*ethoxycarbonyl*-5-*methoxycarbonyl*-3,4-*dihydro*-2(1H)-*pyridone* **13i**. This compound was obtained after 10 h in 74% yield, m.p. 198–200 °C (MeOH–H_2O) (Found: C, 58.45; H, 4.7; N, 8.95. $C_{23}H_{22}ClN_3O_6$ requires C, 58.55; H, 4.65; N, 8.9); ν_{max}/cm^{-1} 3400, 3300, 2980, 1740, 1710, 1670, 1610, 1520, 1470, 1440, 1320, 1250, 1200, 1170, 800 and 720; δ_H(diastereoisomeric mixture; major isomer) 1.2 (3 H, t, Me), 3.51 (3 H, s, OMe), 3.84 (1 H, d, CH), 4.2 (2 H, m, CH_2O), 4.54 (1 H, d, CH), 7.35 (3 H, d, ArH), 7.54–7.64 (6 H, m, ArH), 8.05 (2 H, d, NH_2) and 11.0 (1 H, br s, NH).

6-*Amino*-1-*benzamido*-3-*ethoxycarbonyl*-5-*methoxycarbonyl*-4-(p-*nitrophenyl*)-3,4-*dihydro*-2(1H)-*pyridone* **13j**. This compound was obtained after 21 h of stirring in 78% yield, m.p. 166–168 °C (MeOH–H_2O) (Found: C, 57.0; H, 4.6; N, 11.6. $C_{23}H_{22}N_4O_8$ requires C, 57.25; H, 4.55; N, 11.6); ν_{max}/cm^{-1} 3400, 3280, 1740, 1670, 1610, 1520, 1450, 1360, 1260, 1200, 1170 and 720; δ_H(diastereoisomeric mixture; major isomer) 1.17 (3 H, t, Me), 3.48 (3 H, s, OMe), 3.92 (1 H, d, CH), 4.16 (2 H, m, CH_2O), 4.63 (1 H, d, CH), 7.08–7.22 (2 H, m, ArH), 7.45–7.53 (3 H, m, ArH), 7.79 (2 H, d, ArH), 8.01 (2 H, d, ArH), 8.12 (2 H, d, NH_2) and 10.6 (1 H, br s, NH).

6-*Amino*-1-*benzamido*-3,5-*diethoxycarbonyl*-4-*phenyl*-3,4-*dihydro*-2(1H)-*pyridone* **13k**. This compound was obtained after 7 h of refluxing in 78% yield, m.p. 179–180 °C (EtOH–H_2O) (Found: C, 63.75; H, 5.6; N, 9.35. $C_{24}H_{25}N_3O_6$ requires C, 63.85; H, 5.55; N, 9.3); ν_{max}/cm^{-1} 3400, 3280, 2980, 1730, 1710, 1690, 1660, 1610, 1510, 1470, 1330, 1300, 1250, 1200, 1170 and 700; δ_H(diastereoisomeric mixture) 1.05 (3 H, t, Me), 1.2 (3 H, t, Me), 3.76 (1 H, d, CH), 3.94 (2 H, m, CH_2O), 4.19 (2 H, m, CH_2O), 4.53 (1 H, d, CH), 7.2–7.32 (5 H, m, ArH), 7.51–7.63 (5 H, m, ArH), 8.05 (2 H, d, NH_2) and 11.08 (1 H, br s, NH); δ_C 13.94, 14.39 (2 × Me), 30.68 (C-4), 55.41, 58.5, 61.57, 75.58 (C-3, 2 × CH_2O, C-5), 126.65, 127.51, 128.27 (2-C), 128.32 (2-C), 128.35 (2-C), 128.46, 131.5, 132.39, 142.49 (ArH), 154.19 (C-6) and 162.90, 166.66, 167.85 and 168.23 (4 × CO).

6-*Amino*-1-*benzamido*-3,5-*diethoxycarbonyl*-4-(p-*tolyl*)-3,4-*dihydro*-2(1H)-*pyridone* **13l**. This compound was obtained after 10 h of refluxing in 70% yield, m.p. 193–195 °C (EtOH–H_2O) (Found: C, 64.25; H, 5.95; N, 8.95. $C_{25}H_{27}N_3O_6$ requires C, 64.5; H, 5.8; N, 9.05); ν_{max}/cm^{-1} 3400, 3280, 3200, 2980, 1730, 1710, 1690, 1660, 1610, 1510, 1470, 1440, 1320, 1250, 1190, 1170 and 700; δ_H(diastereoisomeric mixture) 1.05 (3 H, t, Me), 1.23 (3 H, t, Me), 2.26 (3 H, s, Me), 3.76 (1 H, d, CH), 4.02 (2 H, d, CH_2O), 4.23 (2 H, m, CH_2O), 4.55 (1 H, d, CH), 7.07–7.2 (3 H, m, ArH), 7.4–7.68 (6 H, m, ArH), 8.14 (2 H, d, NH_2) and 11.0 (1 H, br s, NH); δ_C 14.18, 14.67 (2 × Me), 20.82, 30.73 (Me, C-4), 55.87, 58.74, 61.78 and 75.82 (C-3, 2 × CH_2O, C-5), 128.53 (2 C), 128.59 (4 C), 129.16 (2 C), 131.77, 132.63, 135.89, 139.61 (ArH), 154.45 (C-6) and 163.21, 166.88, 168.15 and 168.53 (4 × CO).

6-*Amino*-1-*benzamido*-3,5-*diethoxycarbonyl*-4-(p-*methoxyphenyl*)-3,4-*dihydro*-2(1H)-*pyridone* **13m**. This compound was obtained after 8 h refluxing in 81% yield, m.p. 187–189 °C (EtOH–H_2O) (Found: C, 62.3; H, 5.7; N, 8.7. $C_{25}H_{27}N_3O_7$ requires C, 62.35; H, 5.6; N, 8.75%); ν_{max}/cm^{-1} 3420, 3400, 3300, 2980, 1730, 1700, 1660, 1610, 1510, 1470, 1320, 1250, 1170 and 700; δ_H(diastereoisomeric mixture) 1.04 (3 H, t, Me), 1.19 (3 H, t, Me), 3.48 (1 H, d, CH), 3.7 (3 H, s, OMe), 3.88 (2 H, m, CH_2O), 4.08 (2 H, m, CH_2O), 4.4 (1 H, d, CH), 6.82 (2 H, d, ArH), 7.13–7.65 (7 H, m, ArH), 8.03 (2 H, d, NH_2), 10.8 and 11.08 (1 H, br s, NH); δ_C 13.98 and 14.46 (2 × Me), 30.72, 54.99 and 55.71 (C-4, CH_3O, C-3), 58.54, 61.54 and 75.96 (2 × CH_2O, C-5), 113.73 (2 C), 128.32 (4 C), 128.63 (2 C), 131.54, 132.44, 134.44 (ArH), 154.09 and 158.06 (C-6, ArH) and 163.04, 166.71, 167.93 and 168.30 (4 × CO).

6-*Amino*-1-*benzamido*-4-(p-*chlorophenyl*)-3,5-*diethoxycarbonyl*-3,4-*dihydro*-2(1H)-*pyridone* **13n**. This compound was obtained after 10 h refluxing in 55% yield, m.p. 193–195 °C (EtOH–H_2O) (Found: C, 59.3; H, 5.0; N, 8.6. $C_{24}H_{24}ClN_3O_6$ requires C, 59.3; H, 4.95; N, 8.85); ν_{max}/cm^{-1} 3400, 3260, 3200, 2980, 1730, 1710, 1700, 1660, 1610, 1510, 1470, 1310, 1240, 1170 and 700; δ_H(diastereoisomeric mixture) 1.06 (3 H, t, Me), 1.2 (3 H, t, Me), 3.81 (1 H, d, CH), 3.9 (2 H, m, CH_2O), 4.17 (2 H, m, CH_2O), 4.52 (1 H, d, CH), 7.24–7.34 (3 H, m, ArH), 7.49–7.64 (6 H, m, ArH), 8.02 (2 H, d, NH_2) and 11.08 (1 H, br s, NH); δ_C 14.0 and 14.48 (2 × Me), 30.75, 55.16, 58.66, 61.73 and 75.28 (C-4, -3, 2 × CH_2O, C-5), 128.30 (2 C), 128.38 (4 C), 128.58 (2 C), 129.58, 131.46, 132.53 and 141.26 (ArH), 154.38 (C-6) and 162.83, 166.81, 167.7 and 168.17 (4 × CO).

6-*Amino*-1-*benzamido*-3,5-*diethoxycarbonyl*-4-(p-*nitrophenyl*)-3,4-*dihydro*-2(1H)-*pyridone* **13o**. This compound was obtained after 5 h of refluxing in 66% yield, m.p. 201–203 °C (EtOH–H_2O) (Found: C, 57.95; H, 4.9; N, 11.25. $C_{24}H_{24}N_4O_8$ requires C, 58.05; H, 4.85; N, 11.3); ν_{max}/cm^{-1} 3400, 3280, 3200, 2980, 1730, 1710, 1700, 1660, 1610, 1520, 1470, 1350, 1320, 1250, 1170 and 700; δ_H(diastereoisomeric mixture; major isomer) 1.03 (3 H, t, Me), 1.19 (3 H, t, Me), 3.49 (1 H, d, CH), 3.96 (2 H, m, CH_2O), 4.14 (2 H, m, CH_2O), 4.66 (1 H, d, CH), 7.49–7.64 (5 H, m, ArH), 7.82 (2 H, m, ArH), 8.03 (2 H, d, ArH), 8.14 (2 H, d, NH_2) and 11.16 (1 H, br s, NH); δ_C 13.94 and 14.3 (2 × Me), 30.67, 54.16, 58.07, 61.82 and 74.78 (C-4, -3, 2 × CH_2O, C-5), 123.01, 123.98, 128.06, 128.59, 128.80, 128.90, 129.48, 131.31, 131.89, 132.98, 146.51 and 150.10 (ArH), 154.63 (C-6) and 162.40, 166.77, 167.30 and 168.39 (4 × CO).

7-*Aryl*-6-*cyano*-8-*methoxycarbonyl*-2-*methyl*-3H-[1,2,4]*triazolo*[1,5-a]*pyridine*-5-*ones* **15**: *General Procedure*.—1,6-Diamino-4-aryl-3-cyano-5-methoxycarbonyl-2(1H)-pyridone **14** (1.4 mmol) was suspended in acetic anhydride (5 cm^3) and the reaction mixture refluxed for 2 h. With time, a solid precipitated and the reaction mixture was stirred at room temperature overnight. The precipitate was then filtered off and recrystallized from the appropriate solvent.

6-*Cyano*-8-*methoxycarbonyl*-2-*methyl*-7-*phenyl*-3H-[1,2,4]-*triazolo*[1,5-a]*pyridin*-5-*one* **15a**. This compound was obtained in 51% yield, m.p. 299–300 °C (EtOH) (Found: C, 62.25; H, 3.95; N, 18.1. $C_{16}H_{12}N_4O_3$ requires C, 62.35; H, 3.9; N, 18.2); ν_{max}/cm^{-1} 3300–2500, 2960, 2220, 1730, 1700, 1680, 1570, 1500, 1450, 1380, 1200, 1140 and 700; δ_H 2.58 (3 H, s, Me), 3.48 (3 H, s, OMe) and 7.26–7.46 (5 H, m, ArH); δ_C 11.72 and 51.70 (Me, OMe), 90.60 and 92.12 (C-6, -8), 116.61 (CN), 127.55 (2 C), 127.99 (2 C), 128.54, 137.58 (ArH), 146.86, 153.35, 153.99 and 157.65 (C-7, -2, -8a, -5) and 163.14 (CO_2); *m*/*z* (relative intensity) 308 (M^+, 1), 295 (100), 265 (79), 239 (1) and 147 (9).

6-*Cyano*-8-*methoxycarbonyl*-2-*methyl*-7-(p-*tolyl*)-3H-[1,2,-4]-*triazolo*[1,5-a]*pyridin*-5-*one* **15b**. This compound was obtained in 46% yield, m.p. 324–325 °C (EtOH) (Found: C, 63.1; H, 4.4; N, 17.25. $C_{17}H_{14}N_4O_3$ requires C, 63.35; H, 4.35; N, 17.4); ν_{max}/cm^{-1} 3300–2500, 2960, 2220, 1730, 1700, 1570, 1500, 1450, 1380, 1200, 1140 and 700; δ_H 2.39 (3 H, s, Me), 2.57 (3 H, s, Me), 3.51 (3 H, s, OMe), 7.16 (2 H, d, ArH) and 7.26 (2 H, d, ArH); δ_C 11.77 (Me-triazolo), 21.15 and 51.78 (Me, OMe), 90.00 and 92.22 (C-6, -8), 116.80 (CN), 127.60 (2 C), 128.61 (2 C), 134.62 and 137.92 (ArH), 146.88, 153.37, 154.07 and 157.79 (C-7, -2, -8a, -5) and 163.20 (CO_2).

6-*Cyano*-8-*methoxycarbonyl*-7-(p-*methoxyphenyl*)-2-*methyl*-3H-[1,2,4]*triazolo*[1,5-a]*pyridin*-5-*one* **15c**. This compound was obtained in 45% yield, m.p. 298–299 °C (MeCN) (Found: C, 60.25; H, 4.4; N, 16.8. $C_{17}H_{14}N_4O_4$ requires C, 60.35; H, 4.15; N, 16.55); ν_{max}/cm^{-1} 3300–2500, 2960, 2220, 1730, 1700, 1570, 1500, 1450, 1380, 1200, 1140 and 700; δ_H 2.57 (3 H, s, Me), 3.52 (3 H, s, OMe), 3.82 (3 H, s, OMe), 7.01 (2 H, d, ArH) and 7.21 (2 H, d, ArH).

7-(p-*Chlorophenyl*)-6-*cyano*-8-*methoxycarbonyl*-2-*methyl*-3H-[1,2,4]*triazolo*[1,5-a]*pyridin*-5-*one* **15d**. This compound was obtained in 87% yield, m.p. 325–326 °C (DMF) (Found: C, 55.9; H, 3.5; Cl, 10.7; N, 16.4. $C_{16}H_{11}ClN_4O_3$ requires C, 56.05; H, 3.2; Cl, 10.35; N, 16.35); ν_{max}/cm^{-1} 3300–2500, 2960, 2220, 1730, 1700, 1570, 1500, 1450, 1380, 1300, 1250, 1200, 1140 and 700; δ_H 2.58 (3 H, s, Me), 3.54 (3 H, s, OMe), 7.31 (2 H, d, ArH) and 7.53 (2 H, d, ArH).

6-*Cyano*-8-*methoxycarbonyl*-2-*methyl*-7-(p-*nitrophenyl*)-3H-[1,2,4]*triazolo*[1,5-a]*pyridin*-5-*one* **15e**. This compound was obtained in 56% yield, m.p. 299–300 °C (MeCN) (Found: C, 54.4; H, 3.25; N, 20.1. $C_{16}H_{11}N_5O_5$ requires C, 54.4; H, 3.1; N, 19.85); ν_{max}/cm^{-1} 3300–2500, 2960, 2220, 1730, 1700, 1600, 1570, 1500, 1420, 1350, 1300, 1250, 1200, 1140 and 700; δ_H 2.6 (3 H, s, Me), 3.54 (3 H, s, OMe), 7.6 (2 H, d, ArH) and 8.34 (2 H, d, ArH); δ_C 11.83 and 52.01 (Me, OMe), 90.10 and 92.03 (C-6, -8), 116.38 (CN), 123.39 (2 C), 129.28 (2 C), 144.74, 146.97 (ArH), 147.60, 153.74, 153.91 and 155.62 (C-6, -2, -8a, -5) and 162.68 (CO_2).

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