Unexpected Reaction Course of 3-Amino-5-aryl-1*H*-pyrazoles with Dialkyl Dicyanofumarates

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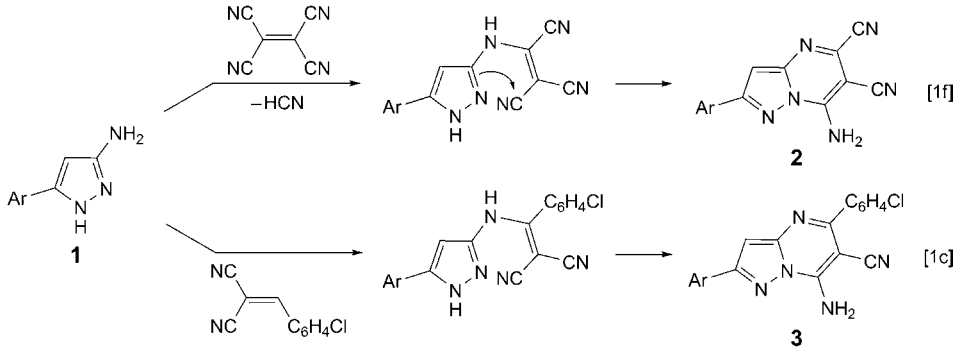
On treatment of 3-amino-5-aryl-1*H*-pyrazoles **1** with dialkyl dicyanofumarates (=(*E*)-but-2-enedioates) **4** in boiling 1,2-dichloroethane, two competitive reactions occurred leading to 3-aryl-5-cyano-6,7-dihydro-6-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylates **10** and 7-amino-2-arylpyrazolo[1,5-*a*]pyrimidine-5,6-dicarboxylates **11**. In DMF at room temperature, as well as at 100°, only compounds **10** were isolated. The formation of the major products of type **10** was rationalized *via Michael* addition of **1** as a *C*(*4*)-nucleophile onto **4**, followed by HCN elimination and lactamization. On the other hand, the minor products **11** result from a *Michael* addition of **1** onto **4** *via* the NH_2 group, and subsequent HCN elimination and cyclization. The structures of the products have been established by X-ray crystallography.

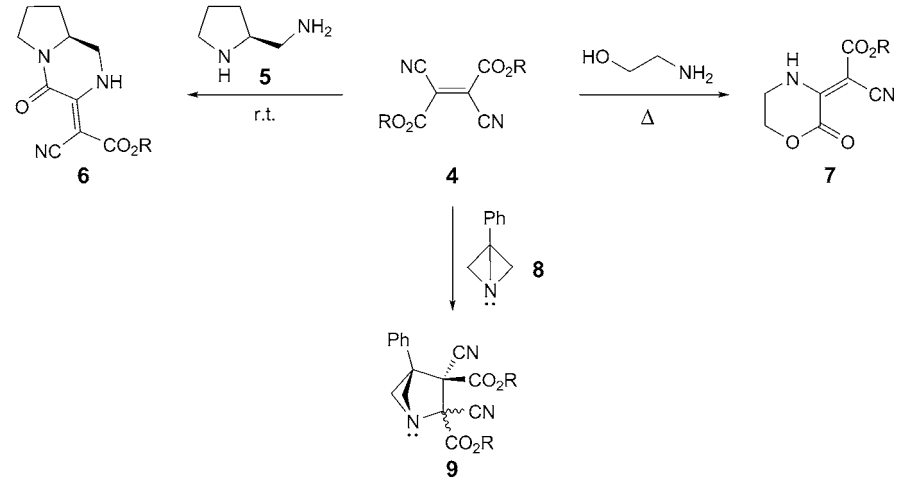
1. Introduction. – The importance of 3-amino-5-arylpyrazoles **1** as valuable building blocks for the synthesis of various fused heterocycles is well-documented in original articles [1] as well as in patents [2]. In addition, modifications of the structure at the NH_2 group were performed in many instances to obtain biologically active products [1c][3]. In some cases, amino-pyrazoles **1** were used as *Michael* donors in reactions with substrates such as tetracyanoethene (TCNE) [1h] or a benzylidenemalononitrile derivative [1e]. In both cases, the reaction was initiated by the attack of the NH_2 group onto the electron deficient C=C bond, and an analogous addition/elimination/cyclization mechanism led to pyrazole[2,3-*a*]pyrimidine derivatives **2** and **3**, respectively (*Scheme 1*).

In a series of recent publications, we reported on reactions of electron-deficient dialkyl dicyanofumarates (=(*E*)-but-2-enedioates) **4** with amines [4], diamines [5], and *β*-amino alcohols [6]. Whereas, in the case of primary and secondary amines, enamines were formed as (*Z*)- and (*E*)-isomers, respectively, *via* an addition/elimination sequence, the reactions with 1,2-diamines yielded cyclic products after subsequent lactamization of the intermediate amino ester. For example, [(*S*)-pyrrolidin-2-yl]methylamine (**5**) reacted smoothly with **4a** (R = Me) to give the bicyclic product **6** [5] (*Scheme 2*). Heating *β*-amino alcohols with **4a** led to morpholin-

Scheme 1



Scheme 2



2-one derivatives **7**. In this case, the stepwise reaction was terminated by lactonization [6].

Finally, reactions of **4** with 3-phenyl-1-azabicyclo[1.1.0]butane (**8**) proceeded at room temperature to yield a 3 : 1 mixture of *cis*- and *trans*-1-azabicyclo[1.1.1]pentane-2,3-dicarboxylates **9** [7].

The aim of the present study was to examine the reaction of **4** with selected 3-amino-5-aryl-1*H*-pyrazoles **1** as reaction partners possessing four potential nucleophilic centers. Previously, the structures of **1** were studied by means of different techniques, and tautomeric equilibria of **1** both in solution and in the solid state have been discussed [8]. The presence of different tautomeric forms of **1** in solution may result in their ambivalent reactivity towards electrophilic reagents such as *Michael* acceptors.

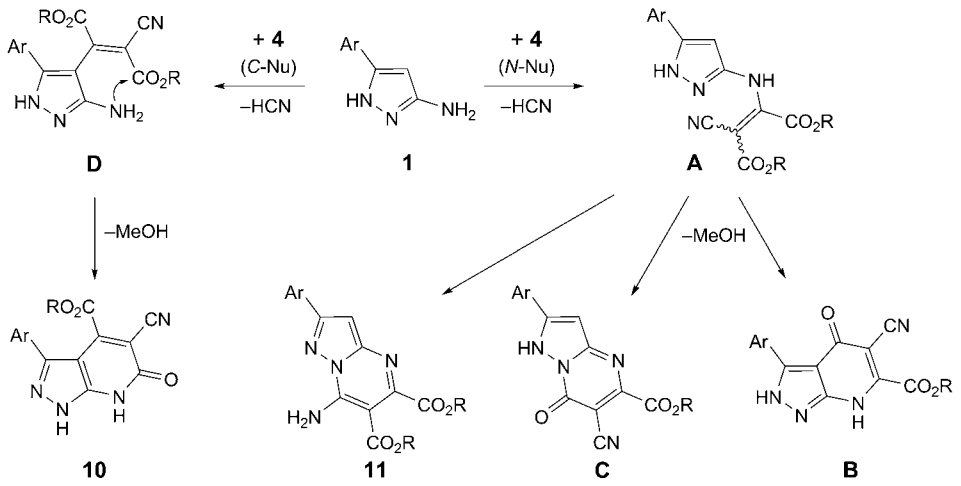
2. Results and Discussion. – Reactions of equimolar amounts of **1** and **4** were carried out in boiling 1,2-dichloroethane ($ClCH_2CH_2Cl$; *Method A*), in DMF at room

temperature (*Method B*), or in DMF at 100° (*Method C*). Using *Method A*, the progress of the reaction was monitored by TLC, which showed that the conversion of the starting materials was complete after 2 h. The ^{1}H-NMR control of the crude mixture obtained after evaporation of the solvent evidenced the presence of two products containing one and two ester groups, respectively. In all cases, the monoester was the major component, which could easily be separated by trituration of the mixture with MeOH or acetone, and subsequent filtration of the precipitate. The minor products obtained from the reactions of **4** with 3-amino-5-(4-methylphenyl)-1*H*-pyrazole (**1a**), containing two ester groups (^{1}H-NMR), were isolated after chromatographic separation (PLC) of the mother liquors obtained after filtration of the major component. Alternatively, when DMF was employed using *Methods B* or *C*, the obtained mixtures were diluted with H_2O, and the products precipitated thereby were filtered and found to be identical with the major component of the reaction performed in boiling $ClCH_2CH_2Cl$ (*Method A*).

The structure of the major product **10a** obtained from the reaction of **1a** and **4a** (R = Me) in boiling $ClCH_2CH_2Cl$ (*Method A*) was proposed on the basis of the spectroscopic data. The ^{1}H-NMR spectrum ((D$_6$)DMSO) revealed the presence of only one MeO group, but no signal of H–C(4) of the pyrazole ring was observed. In the ^{13}C-NMR spectrum ((D$_6$)DMSO), signals characteristic for MeO (53.3 ppm), CN (115.0 ppm), and two C=O groups (160.2 and 163.7 ppm) were detected. All signals for the other sp^2-C atoms appeared between 100 and 150 ppm with low intensities and broadening. The presence of the C≡N group, as well as an ester and an amide C=O group, was confirmed by strong IR-absorption bands (KBr) at 2229, 1740, and 1659 cm^{-1}. The molecular mass *m*/*z* 308 corresponded to the formula $C_{16}H_{12}N_4O_3$, evidencing a product formed after elimination of HCN and MeOH.

For the elucidation of the structures of the isolated products, different reaction pathways presented in *Scheme 3* can be postulated. As mentioned in the *Introduction*,

Scheme 3



3-amino-1*H*-pyrazoles **1** are expected to react as multivalent reagents. Based on the published reactions [1e][1h], one could expect a nucleophilic addition of the NH_2 group of **1** to **4**, followed by elimination of HCN to give the 'enamine-type' product **A**. This intermediate could undergo cyclizations with one of the ester groups, leading, after elimination of MeOH, to the six-membered rings **B** or **C** *via C*- or *N*-nucleophilic attack, respectively. Structure **C** can be eliminated, as the collected data do not indicate the presence of a pyrazole H-C fragment. In contrast to **C**, structure **B** can be considered as a likely product of the reaction. On the other hand, an alternative reaction pathway *via C*-nucleophilic addition of **1** to **4** would lead to intermediate **D**, which subsequently could undergo lactamization to give the pyrazolo[3,4-*b*]pyridine-4-carboxylate **10** (*Table 1)*.

Table 1. *Reactions of* **1** *with Dialkyl Dicyanofumarates* **4**

1 Ar	**4** R	Reaction conditions[a])	**10** (Yield [%])	**11** (Yield [%])
a 4-Me–C_6H_4	**a** Me	*A*; *B*	**a** (75; 90)	**a** (10; 0)
	b Et	*A*; *B*	**b** (81; 91)	**b** (13; 0)
	c ^{i}Pr	*A*; *B*	**c** (66; 77)	**c** (10; 0)
b Ph	**a** Me	*A*; *B*	**d** (53; 90)	
	b Et	*C*	**e** (81)	
	c ^{i}Pr	*C*	**f** (68)	
c 4-Cl–C_6H_4	**a** Me	*C*	**g** (79)	
	b Et	*C*	**h** (67)	
	c ^{i}Pr	*C*	**i** (70)	
d 4-CF_3–C_6H_4	**a** Me	*A*	**k** (38)	

[a]) *Method A:* boiling $ClCH_2CH_2Cl$, 2 h; *Method B:* DMF, r.t., 16 h; *Method C:* DMF, 100°, 11 h.

The spectroscopic data mentioned above did not allow us to distinguish structures **B** and **10**. Therfore, X-ray crystal-structure determinations of the analogous products **10d** and **10k**, obtained from the reactions of **1b** and **1d**, respectively, with **4a**, were performed and established the structures **10d** and **10k** unambiguously (*Fig. 1*). It should be mentioned that the two structures in the crystals represent two different tautomers, as, in **10d**, the H-atom is located at N(7) whereas it is at N(6) in **10k**.

Analogous compounds of type **10** were obtained as major products from the reactions of **1a**–**1d** with **4a**–**4c** (*Table 1*, *Methods A*–*C*). In the reactions of **1a** with **4a**–**4c**, the mother liquors obtained after filtration of the major products **10a**–**10c** were subjected to preparative TLC, and the minor products **11** were isolated as less polar materials[1]). In all cases, the NMR spectra indicated the presence of two ester groups and H–C(4) of the pyrazole ring. Furthermore, strong IR absorptions at *ca*. 1750 and 1685 cm^{-1} correspond well with those observed for enamines obtained from reactions of **4** with primary amines [4]. In addition, in the case of **11a**, a strong absorption at 3115 cm^{-1} could be attributed to a NH_2 group. Indeed, the absence of the signal of the

[1]) The ratio of products **10a** and **11a** did not change when heating of the reaction mixture was extended to 5 h. In an additional experiment, a sample of **11a** was heated in boiling $ClCH_2CH_2Cl$ in the presence of a catalytic amount of TsOH. Even after 3 h, unchanged starting material was recovered quantitatively.

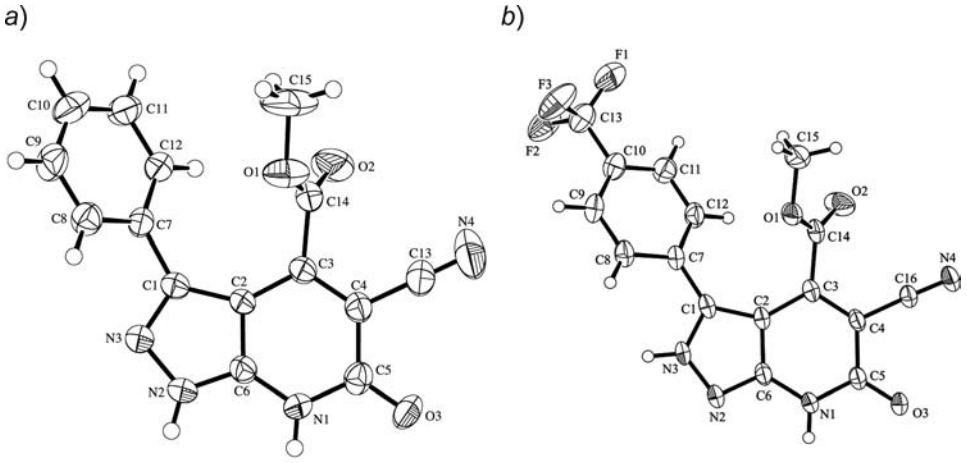


Fig. 1. *ORTEP Plots* [9] *of the molecular structures of* a) **10d** *and* b) *one of the disordered conformations of* **10k** (CF_3 disorder; 50% probability ellipsoids; arbitrary numbering of the atoms)

CN group in the ^{13}C-NMR spectrum of this product suggested that CN in the intermediate **A** was converted by heterocyclization to the C–NH_2 function. These data suggested that this product was formed *via* the competitive reaction of the NH_2 group of **1** with **4** (*Scheme 3*). In analogy to the described reaction pathway with TCNE [1h], this initial step led to the formation of intermediate **A**, which subsequently underwent heterocyclization by nucleophilic attack of the pyrazole N-atom onto the CN group, resulting in the formation of a pyrazolo[1,5-*a*]pyrimidine derivative of type **11**. Apparently, in the intermediate **A** the two ester groups are '*cis*-oriented' ((*E*)-configuration), because this orientation is necessary for the cyclization to give **11**. Finally, an X-ray crystal-structure determination was carried out for **11c**, which established the structure of the pyrazolo[1,5-*a*]pyrimidine (*Scheme 3*, *Fig. 2*).

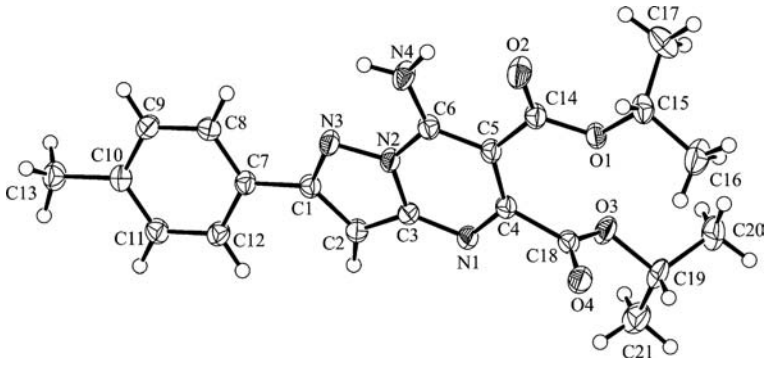


Fig. 2. *ORTEP Plot* [9] *of the molecular structure of* **11c** (50% probability ellipsoids; arbitrary numbering of the atoms)

3. Conclusions. – In contrast to typical aliphatic and aromatic primary amines, 3-amino-5-aryl-1*H*-pyrazoles **1** react as ambivalent reagents with dialkyl dicyanofumarates **4**, preferentially acting as *C*-nucleophiles, and the formed intermediates of type **D** smoothly undergo lactamization to yield pyrazolo[3,4-*b*]pyridin-2-ones **10** in a selective manner. The competitive *Michael* addition of the NH_2 group of **1** onto **4** and subsequent heterocylization *via N*-nucleophilic attack onto the CN group results in the formation of **11**. Whereas reactions of **1** *via* the NH_2 group are common, the reaction initiated by the predominant *C*-nucleophilic attack is observed rather rarely [10]. It is especially worth mentioning that the reactions of **1** with **4** occur differently than the reported reactions with tetracyanoethene, in which the only reported products are formed *via* initial *N*-nucleophilic attack exclusively [1h].

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Experimental Part

1. *General*. M.p.: *MEL-TEMP. II* (*Aldrich*); uncorrected. IR Spectra: *NEXUS* FT-IR instrument; in KBr or as film; $\tilde{\nu}$ in cm^{-1}. ^1H- and ^{13}C-NMR spectra: *Bruker Avance III* instrument (600 and 150 MHz, resp.) using solvent signals as reference; in $CDCl_3$ or $(D_6)DMSO$; δ in ppm, *J* in Hz, the majority of the ^{13}C signals were assigned with the aid of DEPT spectra. HR-ESI-MS: *Bruker maXis* spectrometer; in *m*/*z*.

2. *Starting Materials.* 3-Amino-5-aryl-1*H*-pyrazoles **1a**–**1d** were prepared starting from 3-aryl-3-oxopropanenitrile and $NH_2NH_2 \cdot H_2O$, according to known protocols [11]. Dialkyl dicyanofumarates **4a**–**4c** were obtained from the corresponding alkyl cyanoacetates by reaction with $SOCl_2$ [12]. The $SOCl_2$ used for this reaction must be of 'gold-labeled' quality, or freshly purified by distillation over quinoline and linseed oil [13]. 1,2-Dichloroethane was used as a commercially available material and distilled over K_2CO_3 prior to use. DMF was used as a commercial solvent without additional purification.

3. *Reactions of 3-Amino-5-aryl-*1*H-pyrazoles* **1** *with Dialkyl Dicyanofumarates* **4**. *Method A.* A soln. of the corresponding 3-amino-1*H*-pyrazole **1** (1 mmol) and dialkyl dicyanofumarate **4** (1 mmol) in $ClCH_2CH_2Cl$ (2 ml) was heated at reflux. The progress of the reaction was monitored by TLC, and in all cases complete conversion of **1** was evidenced after 2 h. Then, the solvent was evaporated, and the obtained residue was triturated with a small amount of MeOH. After 1 h at r.t., the precipitated yellowish major product **10** was filtered and purified by recrystallization from EtOH. The mother liquor collected after filtration of **10** was evaporated and separated by prep. TLC (silica gel, CH_2Cl_2/MeOH 99 : 1). After repeated development, the minor products **11** were isolated as less polar fractions (R_f *ca.* 0.80), and small amounts of **10** were also separated as the more polar fractions (R_f *ca.* 0.15). Products **11** were purified by crystallization from MeOH/CH_2Cl_2, and the combined portions of **10** were obtained as anal. pure samples after recrystallization from alcoholic solns.

Method B. A soln. containing **1** (1 mmol) and an equimolar amount of dialkyl dicyanofumarate **4** in DMF (2 ml) was placed in a closed 25-ml round-bottomed flask and kept at r.t. overnight. Then, H_2O (10 ml) was added, and the formed suspension was magnetically stirred at r.t. for *ca.* 1 h. The precipitated yellowish solid was separated by filtration using a paper filter, dried, and purified by recrystallization from an alcoholic soln. In this procedure, the mother liquor obtained after filtration of **10** was not analyzed, and no additional workup was carried out. In the ^1H-NMR spectra of the crude products **10**, signals corresponding to trace amounts of products **11** were also observed. After recrystallization from an alcoholic soln., products **10** were obtained as anal. pure samples.

Method C. Analogous to *Method B*, but the DMF soln. was heated to 100° for 4 to 11 h.

*Methyl 5-Cyano-6,7-dihydro-3-(4-methylphenyl)-6-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10a**). Yield: 230 mg (75%; *Method A*) and 278 mg (90%; *Method B*). Yellow crystals. M.p. 308–312° (dec., EtOH). IR (KBr): 3365–2926v*s* (br., NH), 2229*m* (CN), 1740*s* (C=O), 1659v*s* (br., C=O),

1608*m*, 1513*m*, 1466*m*, 1364*m*, 1252*s*, 1132*w*, 1012*w*, 823*m*, 674*m*, 559*m*. ^{1}H-NMR ((D$_6$)DMSO): 2.37 (*s*, Me); 3.47 (*s*, MeO); 7.29, 7.36 (*AB*, J_{AB} = 7.9, 4 arom. H); 12.83, 14.11 (2 br. *s*, 2 NH). ^{13}C-NMR ((D$_6$)DMSO): 21.2 (Me); 53.3 (MeO); 115.0 (CN); 128.5, 129.7 (4 arom. CH); 100.0, 125.1, 140.0, 141.6, 146.3, 150.2 (6 signals for 7 sp^2 C); 160.2 (br.), 163.7 (2 C=O). HR-ESI-MS: 331.08008 ([M + Na]$^+$, $C_{16}H_{12}N_4NaO_3^+$; calc. 331.08016).

*Dimethyl 7-Amino-2-(4-methylphenyl)pyrazolo[1,5-*a*]pyrimidine-5,6-dicarboxylate* (**11a**). Yield: 32 mg (10%; *Method A*). Colorless crystals. M.p. 258–260° (hexane/CH_2Cl_2). IR (KBr): 3415*s* (br., NH), 3314*s* (NH_2), 2951*w*, 1755*s* (C=O), 1684*s* (C=O), 1632*s* , 1611*m*, 1591*s*, 1570*m*, 1539*w*, 1453*m*, 1437*m*, 1326*s*, 1313*m*, 1241*s*, 1213*m*, 1092*w*, 1029*w*, 802*s*, 621*m*. ^{1}H-NMR ($CDCl_3$): 2.40 (*s*, Me); 3.89, 3.97 (2*s*, 2 MeO); 6.83 (*s*, H–C(3)); 7.18 (br. *s*, NH); 7.27, 7.85 (*AB*, J_{AB} = 8.0, 4 arom. H); 8.58 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 21.4 (Me); 52.3, 52.9 (2 MeO); 95.9 (C(3)); 126.6, 129.5 (4 arom. CH); 88.7, 129.1, 139.8, 147.9, 149.4, 152.4, 158.1 (7 signals for 7 sp^2 C); 165.9, 166.8 (2 C=O). HR-ESI-MS: 363.10674 ([M + Na]$^+$, $C_{17}H_{16}N_4NaO_4^+$; calc. 363.10638).

*Ethyl 5-Cyano-6,7-dihydro-3-(4-methylphenyl)-6-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10b**). Yield: 260 mg (81%; *Method A*), and 295 mg (91%; *Method B*). Yellowish powder. M.p. 290–294° (dec., MeOH). IR (KBr): 3382–2803v*s* (br., NH), 2228*m* (CN), 1739*s* (C=O), 1663v*s* (br., C=O), 1617*m*, 1512*s*, 1467*s*, 1375*m*, 1352*w*, 1243v*s*, 1188*m*, 1018*m*, 823*m*, 719*w*, 683*w*, 557*m*. ^{1}H-NMR ((D$_6$)DMSO): 0.89 (*t*, J = 7.2, *Me*CH$_2$); 2.37 (*s*, MeC$_{Ar}$); 3.95 (*q*, J = 7.2, MeC*H*$_2$); 7.18, 7.36 (*AB*, J_{AB} = 8.0, 4 arom. H); 12.82, 14.13 (2 br. *s*, 2 NH). ^{13}C-NMR ((D$_6$)DMSO): 13.2 (*Me*CH$_2$); 21.1 (*Me*C$_{Ar}$); 63.0 (MeCH$_2$); 114.8 (CN); 128.4, 129.2 (4 arom. CH); 99.2, 124.9, 140.0, 141.3, 146.5, 150.4 (6 signals for 7 sp^2 C); 159.9 (br.), 163.0 (2 C=O). HR-ESI-MS: 345.09599 ([M + Na]$^+$, $C_{17}H_{14}N_4NaO_3^+$; calc. 345.09581).

*Diethyl 7-Amino-2-(4-methylphenyl)pyrazolo[1,5-*a*]pyrimidine-5,6-dicarboxylate* (**11b**). Yield: 50 mg (13%; *Method A*). Colorless crystals. M.p. 218–220° (hexane/CH_2Cl_2). IR (KBr): 3382*s* (br., NH), 3287*s* (br., NH_2), 2987*w*, 2975*w*, 1741*s* (C=O), 1683*s* (C=O), 1635*s*, 1595*s*, 1569*m*, 1540*w*, 1453*w*, 1393*w*, 1318*s*, 1236v*s*, 1213*m*, 1087*m*, 1025*w*, 799*m*. ^{1}H-NMR ($CDCl_3$): 1.35, 1.43 (2*t*, J = 7.2, 2 *Me*CH$_2$); 2.40 (*s*, MeC$_{Ar}$); 4.35, 4.43 (2*q*, J = 7.2, 2 MeC*H*$_2$); 6.83 (*s*, H–C(3)); 7.19 (br. *s*, NH); 7.28, 7.86 (*AB*, J_{AB} = 8.1, 4 arom. H); 8.70 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 14.0, 14.1 (2 *Me*CH$_2$); 21.3 (*Me*C$_{Ar}$); 61.4, 62.1 (2 MeCH$_2$); 95.6 (C(3)); 126.5, 129.5 (4 arom. CH); 87.8, 129.1, 139.7, 147.9, 149.5, 152.6, 157.9 (7 signals for 7 sp^2 C); 165.7, 166.4 (2 C=O). HR-ESI-MS: 391.13812 ([M + Na]$^+$, $C_{19}H_{20}N_4NaO_4^+$; calc. 391.13768).

*1-Methylethyl 5-Cyano-6,7-dihydro-3-(4-methylphenyl)-6-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10c**). Yield: 222 mg (66%; *Method A*) and 260 mg (77%; *Method B*). Yellow powder. M.p. 254–257° (dec., MeOH). IR (KBr): 3439–2750v*s* (br., NH), 2230*m* (CN), 1734*s* (C=O), 1661v*s* (br., C=O), 1620*m*, 1513*m*, 1466*m*, 1375*m*, 1249*s*, 1102*m*, 1006*m*, 847*w*, 823*m*, 683*w*, 557*w*. ^{1}H-NMR ((D$_6$)DMSO): 1.01 (*d*, J = 6.6, *Me*$_2$CH); 2.37 (*s*, MeC$_{Ar}$); 4.80–4.82 (*m*, Me$_2$C*H*); 7.32–7.35 (*m*, 4 arom. H); 12.81, 14.12 (2 br. *s*, 2 NH). ^{13}C NMR ((D$_6$)DMSO): 20.8 (*Me*$_2$CH); 21.1 (*Me*C$_{Ar}$); 71.6 (Me$_2$*C*H); 114.8 (CN); 128.5, 129.5 (4 arom. CH); 99.3, 124.8, 140.1, 141.5, 146.9, 150.4 (6 signals for 7 sp^2 C); 160.0 (br.), 162.9 (2 C=O). HR-ESI-MS: 359.11123 ([M + Na]$^+$, $C_{18}H_{16}N_4NaO_3^+$; calc. 359.11146).

*Bis(1-methylethyl) 7-Amino-2-(4-methylphenyl)pyrazolo[1,5-*a*]pyrimidine-5,6-dicarboxylate* (**11c**). Yield: 41 mg (10%; *Method A*). Colorless crystals. M.p. 162–164° (hexane/CH_2Cl_2). IR (KBr): 3420*m* (br., NH), 3315*m* (br., NH_2), 2980*m*, 2934*w*, 1738*s* (C=O), 1677v*s* (C=O), 1614*m*, 1593v*s*, 1571*m*, 1455*m*, 1372*m*, 1334*m*, 1313*m*, 1244*s*, 1214*m*, 1166*m*, 1105*s*, 1019*m*, 798*m*. ^{1}H-NMR ($CDCl_3$): 1.36 (*d*, J = 6.0, *Me*$_2$CH); 1.44 (*d*, J = 6.6, *Me*$_2$CH); 2.40 (*s*, MeC$_{Ar}$); 5.23–5.28 (*m*, 2 Me$_2$C*H*); 6.84 (*s*, H–C(3)); 7.18 (br. *s*, NH); 7.28, 7.86 (*AB*, J_{AB} = 7.9, 4 arom. H); 8.71 (br. *s*, NH). ^{13}C-NMR ($CDCl_3$): 21.4 (*Me*C$_{Ar}$); 21.7, 21.8 (2 *Me*$_2$CH); 69.6, 70.0 (2 Me$_2$*C*H); 95.5 (C(3)); 126.5, 129.5 (4 arom. CH); 88.1, 129.2, 139.6, 147.9, 149.5, 152.9, 157.8 (7 signals for 7 sp^2 C); 165.3, 165.9 (2 C=O). HR-ESI-MS: 419.16950 ([M + Na]$^+$, $C_{21}H_{24}N_4NaO_4^+$; calc. 419.16898).

*Methyl 5-Cyano-6,7-dihydro-6-oxo-3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10d**). Yield: 157 mg (53%; *Method A*) and 265 mg (90%; *Method B*). Yellowish powder. M.p. 324–330° (dec., MeOH). IR (KBr): 3367–2795v*s* (br., NH), 2226*m* (CN), 1746*s* (C=O), 1659v*s* (br., C=O), 1618*m*, 1545*m*, 1511*s*, 1466*s*, 1365*m*, 1247v*s*, 1138*w*, 1026*s*, 866*m*, 763*m*, 701*m*, 669*m*, 561*m*. ^{1}H-NMR ((D$_6$)DMSO): 3.42 (*s*, MeO); 7.35–7.45 (*m*, 2 arom. H); 7.50–7.60 (*m*, 3 arom. H); 12.82, 14.12 (2 br. *s*, 2 NH). ^{13}C-NMR ((D$_6$)DMSO): 53.1 (MeO); 114.8 (CN); 128.5, 129.0, 129.9 (5 arom. CH); 100.2, 142.1,

145.8, 150.0 (4 signals for 6 sp^2 C); 160.2 (br.), 163.5 (2 C=O). HR-ESI-MS: 317.06468 ([M + Na]$^+$, $C_{15}H_{10}N_4NaO_3^+$; calc. 317.06451).

*Ethyl 5-Cyano-6,7-dihydro-6-oxo-3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10e**). Yield: 250 mg (81%; *Method C*). Yellow crystals. M.p. 298–302° (dec., EtOH). IR (KBr): 3390–2900v*s* (br., NH), 2231*m* (CN), 1740*s* (C=O), 1678v*s* (br., C=O), 1639*s*, 1565*m*, 1523*w*, 1450*m*, 1344*w*, 1238v*s*, 1177*m*, 1021*m*, 910*m*, 769*m*, 749*m*, 648*w*. ^{1}H-NMR ((D$_6$)DMSO): 0.85 (*t*, *J* = 7.2, *Me*CH$_2$); 3.91 (*q*, *J* = 7.2, MeC*H*$_2$); 7.43–7.51 (*m*, 4 arom. H), 12.88, 14.13 (2 br. *s*, 2 NH). ^{13}C-NMR ((D$_6$)DMSO): 13.1 (*Me*CH$_2$); 62.8 (MeCH$_2$); 114.7 (CN); 128.5, 128.9, 130.0 (5 arom. CH); 99.8, 141.1, 146.5, 150.1 (4 signals for 6 sp^2 C); 159.8, 163.1 (2 C=O). MS: 308 (100, M^+), 235 (27),149 (51), 77 (43). Anal. calc. for $C_{16}H_{12}N_4O_3$ (308.29): C 62.33, H 3.92, N 18.17; found: C 62.24, H 3.85, N 18.23.

*1-Methylethyl 5-Cyano-6,7-dihydro-6-oxo-3-phenyl-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10f**). Yield: 220 mg (68%; *Method C*). M.p. >300° (dec.). 3400–2900v*s* (br., NH), 2229*m* (CN), 1737*s* (C=O), 1678v*s* (br., C=O), 1639*s*, 1564*m*, 1508*m*, 1465*m*, 1374*w*, 1241v*s*, 1179*m*, 1102*m*, 1014*w*, 909*m*, 830*w*, 767*m*, 720*m*, 700*m*, 645*w*, 567*w*. ^{1}H-NMR ((D$_6$)DMSO): 0.99 (*d*, *J* = 6.6, *Me*$_2$CH); 4.79 (*m*, Me$_2$C*H*); 7.45–7.54 (*m*, 5 arom. H); 12.83, 14.14 (2 br. *s*, 2 NH). ^{13}C-NMR ((D$_6$)DMSO): 20.8 (*Me*$_2$CH); 71.5 (Me$_2$CH); 114.7 (CN); 128.6, 128.9, 130.0 (5 arom. CH); 99.6, 141.5, 146.5, 150.1 (4 signals for 6 sp^2 C); 160.1 (br.), 162.8 (2 C=O). MS: 322 (58, M^+), 280 (100), 263 (17), 179 (17), 152 (19), 124 (15), 98 (23), 77 (55). Anal. calc. for $C_{17}H_{14}N_4O_3$ (322.32): C 63.35, H 4.38, N 17.38; found: C 63.49, H 4.25, N 17.31.

*Methyl 3-(4-Chlorophenyl)-5-cyano-6,7-dihydro-6-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10g**). Yield: 260 mg (79%; *Method C*). M.p. 270–272°. IR (KBr): 3450–2850v*s* (br., NH), 2229*m* (CN), 1737*s* (C=O), 1651v*s* (br., C=O), 1509*m*, 1364*m*, 1252*s*, 1092*m*, 1014*m*, 837*s*, 677*m* (br.). ^{1}H-NMR ((D$_6$)DMSO): 3.44 (*s*, MeO); 7.25, 7.30 (*AB*, J_{AB} = 7.9, 4 arom. H). MS: 328 (37, M^+), 139 (100), 111 (35), 75 (33.6). Anal. calc. for $C_{15}H_9ClN_4O_3$ (328.71): C 54.81, H 2.76, N 17.04; found: C 54.71, H 2.69, N 17.11.

*Ethyl 3-(4-Chlorophenyl)-5-cyano-6,7-dihydro-6-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10h**). Yield: 230 mg (67%; *Method C*). M.p. > 300°. IR (KBr): 3382–2800v*s* (br., NH), 2230*w* (CN), 1747*s* (C=O), 1659v*s* (br., C=O), 1467*s*, 1389*m*, 1253v*s*, 1092*m*, 1018*m*, 835*m*, 665*m*. ^{1}H-NMR ((D$_6$)DMSO): 0.87 (*t*, *J* = 7.2, *Me*CH$_2$); 3.88 (*q*, *J* = 7.2, MeC*H*$_2$); 7.10, 7.28 (*AB*, J_{AB} = 8.0, 4 arom. H). MS: 328 (M^+). Anal. calc. for $C_{16}H_{11}ClN_4O_3$ (342.74): C 56.07, H 3.23, N 16.35; found: C 56.07, H 3.23, N 16.35.

*1-Methylethyl 3-(4-Chlorophenyl)-5-cyano-6,7-dihydro-6-oxo-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10i**). Yield: 250 mg (70%; *Method C*). M.p. >300° (dec.). IR (KBr): 3420–2750v*s* (br., NH), 2229*w* (CN), 1728*s* (C=O), 1659v*s* (br., C=O), 1381*m*, 1255*m* (br.), 1095*m*, 1008*w*, 841*m*, 673*m*. ^{1}H-NMR ((D$_6$)DMSO): 0.89 (*t*, *J* = 7.2, *Me*CH$_2$); 2.37 (*s*, MeC$_{Ar}$); 3.95 (*q*, *J* = 7.2, MeC*H*$_2$); 7.18, 7.36 (*AB*, J_{AB} = 8.0, 4 arom. H). MS: 356 (M^+). Anal. calc. for $C_{17}H_{13}ClN_4O_3$ (356.76): C 57.23, H 3.67, N 15.70; found: C 57.35, H 3.75, N 15.62.

*Methyl 5-Cyano-6,7-dihydro-6-oxo-3-[4-(trifluoromethyl)phenyl]-1*H*-pyrazolo[3,4-*b*]pyridine-4-carboxylate* (**10k**). Yield: 140 mg (38%; *Method A*). M.p. 271–280° (dec., MeOH). IR (KBr): 3200–2750v*s* (br., NH), 2247*s* (CN), 1736*s* (C=O), 1656*s* (br., C=O), 1622*m*, 1607*s*, 1501*s*, 1464*m*, 1411*m*, 1362*w*, 1328v*s*, 1258v*s*, 1137*s* (br.), 1068*s*, 1006*m*, 850*m*, 730*w*, 686*m*, 604*w* (br.), 560*w*. ^{1}H-NMR ((D$_6$)DMSO): 3.46 (*s*, MeO); 7.64, 7.92 (*AB*, J_{AB} = 8.4, 4 arom. H); 12.80, 14.15 (2 br. *s*, 2 NH). ^{13}C-NMR ((D$_6$)DMSO): 53.1 (MeO); 114.8 (CN); 125.8, 129.4 (4 arom. CH); 121.5, 126.9, 134.1, 142.0, 144.6, 149.9 (6 sp^2 C); 124.2 (*d*, ^1J(C,F) = 270.8, CF$_3$); 129.8 (*d*, ^2J(C,F) = 32.0, *C*–CF$_3$); 160.8, 163.5 (2 C=O). HR-ESI-MS: 385.0516 ([M + Na]$^+$, $C_{16}H_9F_3N_4NaO_3^+$; calc. 385.0524).

7. *X-Ray Crystal-Structure Determination of* **10b**, **10k**, *and* **11c** (*Table 2* and *Figs. 1* and *2*)[2]). The measurements of **10k** and **11c** were performed on an *Agilent Technologies SuperNova* area-detector diffractometer [14] using CuK_α radiation (λ 1.54184 Å) from a micro-focus X-ray source and an *Oxford Instruments Cryojet XL* cooler, whereas those of **10b** were performed on a *Nonius KappaCCD* area-detector diffractometer [15] using graphite-monochromated MoK_α radiation (λ 0.71073 Å). Data

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[2]) CCDC-913237–913239 contain the supplementary crystallographic data for this article. These data can be obtained free of charge from the *Cambridge Crystallographic Data Centre via* http://www.ccdc.cam.ac.uk/data_request/cif.

Table 2. *Crystallographic Data for Compounds* **10d**, **10k**, *and* **11c**

	10d	**10k**	**11c**
Crystallized from	MeOH	MeOH	hexane/CH_2Cl_2
Empirical formula	$C_{15}H_{10}N_4O_3$	$C_{16}H_9F_3N_4O_3$	$C_{21}H_{24}N_4O_4$
Formula weight [g mol^{-1}]	294.27	362.27	396.44
Crystal color, habit	colorless, prism	yellow, prism	colorless, plate
Crystal dimensions [mm]	unknown	$0.15 \times 0.20 \times 0.20$	$0.07 \times 0.12 \times 0.28$
Temp. [K]	298(1)	160(1)	160(1)
Crystal system	monoclinic	monoclinic	triclinic
Space group	$P2_1/c$	$P2_1/c$	$P\bar{1}$
Z	4	4	2
Reflections for cell determination	2852	4986	26596
2θ Range for cell determination [°]	5–55	6–142	6–149
Unit cell parameters:			
a [Å]	12.6815(4)	11.1763(4)	8.47828(19)
b [Å]	8.7276(4)	9.8855(2)	9.5942(2)
c [Å]	13.5654(6)	15.2144(6)	14.1580(3)
α [°]	90	90	96.3610(17)
β [°]	115.463(4)	111.113(4)	100.4022(17)
γ [°]	90	90	115.294(2)
V [Å^3]	1355.6(1)	1568.10(9)	1000.99(4)
D_x [g cm^{-3}]	1.442	1.534	1.315
Radiation	MoK_α	CuK_α	CuK_α
μ [mm^{-1}]	0.1046	1.160	0.762
Scan type	ω	ω	ω
$2\theta_{(max)}$ [°]	55	142.2	148.8
Transmission factors (min; max)	–	0.464; 1.000	0.033; 1.000
Total reflections measured	5409	13798	37503
Symmetry independent reflections	3047	2966	4038
Reflections with $I > 2\sigma(I)$	1187	2443	3739
Reflections used in refinement	3047	2966	4038
Parameters refined; restraints	201; 0	272; 66	276; 0
Final $R(F)$ [$I > 2\sigma(I)$ reflections]	0.0566	0.0570	0.0364
$wR(F^2)$ (all data)	0.1211	0.1625	0.1022
Weighting parameters [a; b][a])	0.0416; 0	0.0750; 1.7522	0.0525; 0.2666
Goodness-of-fit	0.915	1.055	1.052
Secondary extinction coefficient	0.028(4)	–	0.0159(9)
Final Δ_{max}/σ	0.001	0.001	0.001
$\Delta\rho$ (max; min) [e Å^{-3}]	0.16; −0.17	0.40; −0.48	0.28; −0.19

[a]) $w^{-1} = \sigma^2(F_o^2) + (aP)^2 + bP$ where $P = (F_o^2 + 2F_c^2)/3$.

reduction was performed with CrysAlisPro [14] (for **10k** and **11c**) and HKL Denzo and Scalepack [16] (for **10b**). The intensities were corrected for *Lorentz* and polarization effects, and an empirical absorption correction using spherical harmonics [14] was applied in the cases of **10k** and **11c**. Equivalent reflections were merged. The data collection and refinement parameters are compiled in *Table 2*, and views of the molecules are shown in *Figs. 1* and *2*. The structures were solved by direct methods using SHELXS97 [17] (for **10k** and **11c**) or SIR92 [18] (for **10b**), which revealed the positions of most non-H-atoms. In the case of **10k**, the F-atoms of the CF_3 group are disordered over two orientations. Two sets of positions were defined for these F-atoms and the site occupation factor of the major orientation of the CF_3 group was refined to 0.893(3). Similarity restraints were applied to the chemically equivalent C–F

and F···F distances, while neighboring atoms within and between each conformation of the disordered CF_3 group were restrained to have similar atomic displacement parameters. In all cases, the non-H-atoms were refined anisotropically. The amine H-atoms of **10k** and **11c** were placed in the positions indicated by a difference electron-density map, and their positions were allowed to refine together with individual isotropic displacement parameters. All remaining H-atoms in all structures were placed in geometrically calculated positions and refined by using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent atom (1.5 U_{eq} for Me groups). The refinement of each structure was carried out on F^2 by using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. In the cases of **10d** and **11c**, a correction for secondary extinction was applied. Neutral atom-scattering factors for non-H-atoms were taken from [19a], and the scattering factors for H-atoms were taken from [20]. Anomalous dispersion effects were included in F_c [21]; the values for f' and f'' were those of [19b]. The values of the mass attenuation coefficients are those of [19c]. All calculations were performed using the SHELXL97 [17] program.

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