# The Reaction of Amino-Imidazoles, -Pyrazoles and -Triazoles with $\alpha,\beta$-Unsaturated Nitriles



Sergey A. Komykhov[1*], Konstantin S. Ostras[1], Alvard R. Kostanyan[1], Sergey M. Desenko[1], Valery D. Orlov[2] and Herbert Meier[3]

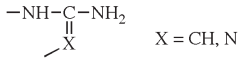
[1]Institute for Single Crystals, UA-61001 Kharkov, Ukraine
e-mail: komykhov@isc.kharkov.com
[2]Kharkov National University, Department of Organic Chemistry, UA-61077 Kharkov, Ukraine
[3]University of Mainz, Institute of Organic Chemistry, D-55099 Mainz, Germany
Received March 14, 2005

The reactions of $\alpha,\beta$-unsaturated nitriles (**1**, **9**, **12**) as bielectrophiles with aminoazoles (**2**, **4**, **6**) as binucleophiles were investigated. Acrylonitrile (**1**) reacts almost exclusively in a chemoselective Michael-type addition yielding the substituted azoles **3**, **5** and **7**, respectively. Cinnamonitriles **9a,b** behave in a similar way, but the free CN group adds a second molecule **4** yielding **10a,b** and its cyclocondensation product **11a,b** as minor component. The attempted formation of azolopyrimidines is best achieved by the reaction of the benzylidenemalononitriles **12a - f** with **2** or **4**. The process is chemo- and regioselective. The structure determinations were based on NMR measurements including DEPT, COSY, ROESY, HMQC and HMBC techniques and correct earlier suggestions.

*J. Heterocyclic Chem.*, **42**, 1111 (2005).

## Introduction.

Various physiological activities were found for natural and synthetic azolopyrimidines [1]. Therefore the preparation of new azolopyrimidine derivatives and their chemical modification represent a perspective trend and a promising goal. The most common method of dihydroazolopyrimidine synthesis is the cyclocondensation of aminoazoles, which contain an amidine substructure with $\alpha,\beta$-unsaturated ketones [2]. Aminoazoles are bifunctional nucleophiles which should react with other bifunctional electrophiles like $\alpha,\beta$-unsaturated nitriles as well. Cyclic products, obtained in the reaction of $\alpha,\beta$-unsaturated nitriles and dinucleophiles as for example hydrazines, have been reported [3]. Thus, in continuation of our study on dihydroazolopyrimidines with active functional groups [4], we investigated the reaction of $\alpha,\beta$-unsaturated nitriles with azoles containing the segment:

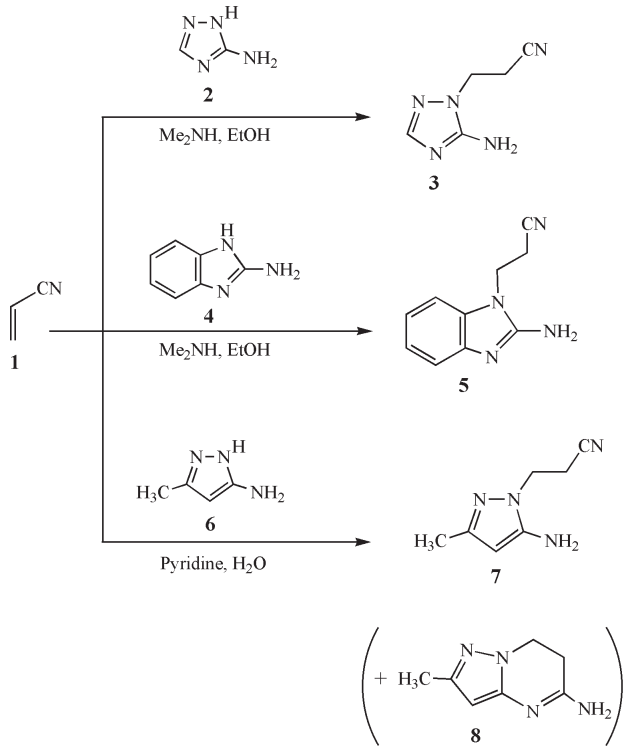



Due to the unsymmetric nitriles, two regioisomers can be expected for X = CH. If additionally three reactive centers (X = N) in an unsymmetric unit are present, altogether four isomers could be generated. Several examples of reaction products of $\alpha,\beta$-unsaturated nitriles and aminoazoles were published by Elnagdi and coworkers [5], Ibrahim [6], Elgemeie [7] and Abdelhamid [8]; however, the reported product structures are not in agreement [6,8]. A profound structure determination, applying modern NMR techniques, seemed us to be necessary.

## Results and Discussion.

The reaction of $\alpha,\beta$-unsaturated nitriles and aminoazoles starts with a Michael-type addition. Acrylonitrile and 3-amino-5-phenylpyrazole for example yield in pyridine/water the $\beta$-adduct [9], the respective pyrazolopyrimidine is not formed. We found now a similar behavior of acryl-onitrile (**1**) and 3-amino-1,2,4-triazole (**2**) [10] or **1** and 2-aminobenzimidazole (**4**) [11]. The products **3** and **5**, respectively, show the typical IR band for the CN group at 2250 ± 5 cm$^{-1}$ and the δ value of 118.4 ± 0.1 ppm for the CN group in the $^{13}$C NMR spectrum. Scheme 1 demonstrates the attack of an endocyclic nitrogen atom of the amidine

Scheme 1



structure of **2** or **4** on the $\beta$-carbon atom of **1**. Whereas **4** is a symmetrical species, **2** has principally two different reactive sites. The attachment of the 2-cyanoethyl group on N-4 of **2** can be excluded since the ring proton does not show a $^3J$ (H,C) coupling to a saturated carbon atom. Dimethylamine in ethanol was used as catalyst for both reactions. A cyclization of **3** or **5** to bicyclic systems could not be found.

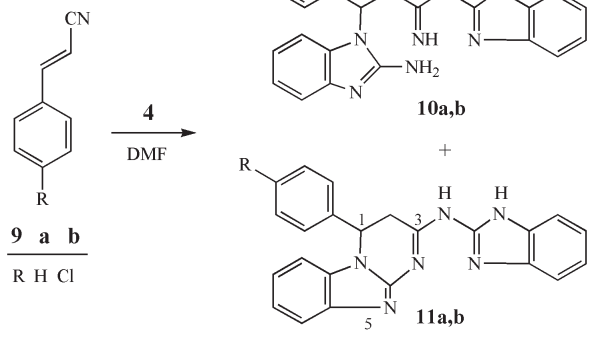
3-Amino-5-methylpyrazole (**6**) [12] reacted with **1** to the $\beta$-adduct **7**; however, the $^1$H NMR spectrum of the raw product revealed the presence of the bicyclic compound **8** as minor component (ratio **7**:**8** = 3:1). The yields of **3**, **5** and **7** were low (10, 35, 37 %), so we refrained from an isolation of **8**.

On the whole, the reactions shown in Scheme 1 are not suitable for the formation of azolopyrimidines.

The next attempt was focused on cinnamonitrile **9a** and its 4-chloro derivative **9b** which were reacted with **4** in DMF (Scheme 2). The major products **10a,b** are 1:2 adducts, whereby one 2-aminobenzimidazole molecule **4** attacks with N-1 in $\beta$-position of the nitrile, whereas the second molecule **4** attacks with the exocyclic amino group at the nitrile carbon atom. The minor reaction products **11a,b** are cyclocondensation products formed by the elimination of $NH_3$. Equimolar mixtures of **9a** and **4** gave in boiling DMF 19 % of **10a** and 4 % of **11a**; analogously 51 % of **10b** and 11 % of **11b** were obtained. Excess amounts of nitriles did not yield 1:1 adducts. This result is in contrast to the reaction of **4** with $\alpha,\beta$-unsaturated ketones as bielectrophiles, which furnished 1:1 adducts [10,11].

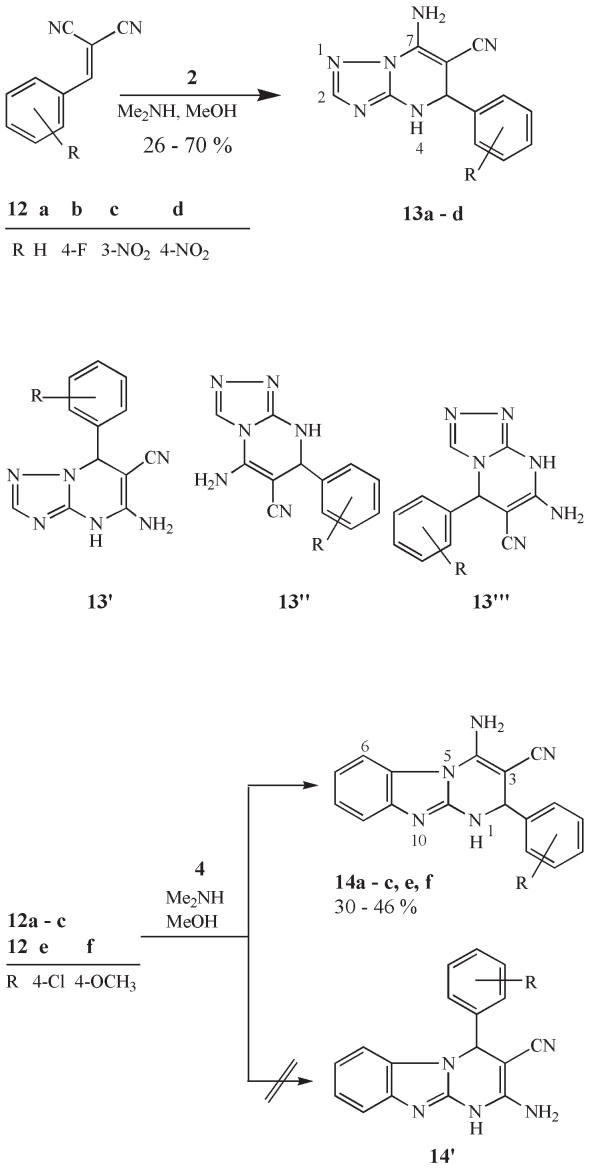
Apart from tautomeric equilibria in the amidine unit, one benzimidazole substructure is symmetric (due to a fast proton transfer), the other appears to be unsymmetric in the $^1$H and $^{13}$C NMR spectra of **9a,b** and **10a,b**.

Scheme 2




Concerning the formation of dihydroazolopyrimidines, the cinnamonitriles in Scheme 2 are an improvement in comparison to acrylonitrile in Scheme 1, but they are not good enough for preparative purposes. Therefore we studied the behavior of benzylidenemalonodinitriles **12a - f**. Their reactivity towards the aminoazoles **2** and **4** proved to be much higher so that mild conditions by heating in methanol in the presence of dimethylamine could be used. Scheme 3 shows the generation of the desired azolopyrimidine derivatives **13** and **14** in reasonable yields.

Scheme 3




The $^1$H and $^{13}$C NMR data of **13** and **14** are summarized in Tables 1 and 2. The $\delta$ values reveal a pyrimidine ring structure which is common to **13** and **14**; nevertheless, there are four possible isomeric structures for the product of **12** and **2**, and two possible structures for the product of **12** and **4** (Scheme 3). A detailed NMR study including one-dimensional NOE, ROESY, COSY, HMQC and HMBC measurements was performed for **14f** for which structure **14'** (R = 4-$OCH_3$) was claimed [6]. Figure 1 shows the HMBC con-

tour plot with particular emphasis on the crosspeaks for 2-H (δ = 5.14). Six correlations can be seen: $^2J$ (2-H, C-3), $^3J$ (2-H, CN), $^3J$ (2-H, *o*-C, Phenyl), $^2J$ (2-H, *i*-C, Phenyl), $^3J$ (2-H, C-4) and $^3J$ (2-H, C-10a). The Nuclear Overhauser effect between the protons of the $NH_2$ group and the aromatic proton 6-H rules structure **14'** out. Thus, the regioselectivity of the addition **12** + **4** is established – in so far as the exocyclic amino group and not the endocyclic nitrogen atom attackes in β-position of the nitrile **4**. A tautomeric form, in which N-10 bears a hydrogen atom instead of N-1 cannot be excluded a priori – particularly not a fast equilibration with **14** – but the NOE between 1-H and 2-H favors strongly structure **14**. Due to a torsional angle close to 90°, the coupling constant between NH and 2-H is small. The signal of 2-H is a singlet, for some compounds a broadened singlet, the largest $^3J$ value amounts to 2.0 Hz measured for **12d**. A complete assignment of all $^1$H and $^{13}$C NMR signals for **14f**, together with the most important NOEs is given in Scheme 4.

The neighborhood (NOE) of 4-NH and 5-CH in the compounds **12** rules the alternative structures **13'** and **13'''** out, **13''** can be excluded by the absence of an NOE between the amino group and the proton on the triazole ring.

The result of the structure elucidation of **13** and **14** which includes the attack of the $NH_2$ group on the β-position of **2** and **4**, respectively, is surprising; it is not only in contrast to the reactivity of **2** and **4** in the presence of **1**, it disproves also the structure of the type **14'** (R = 4-$OCH_3$) which was suggested as reaction product of **12f** and **4** [6]. Recently a three-component reaction of 2-aminobenzimidazole, aromatic aldehydes and malononitril was studied [13]. The published product structures correspond to **14**.

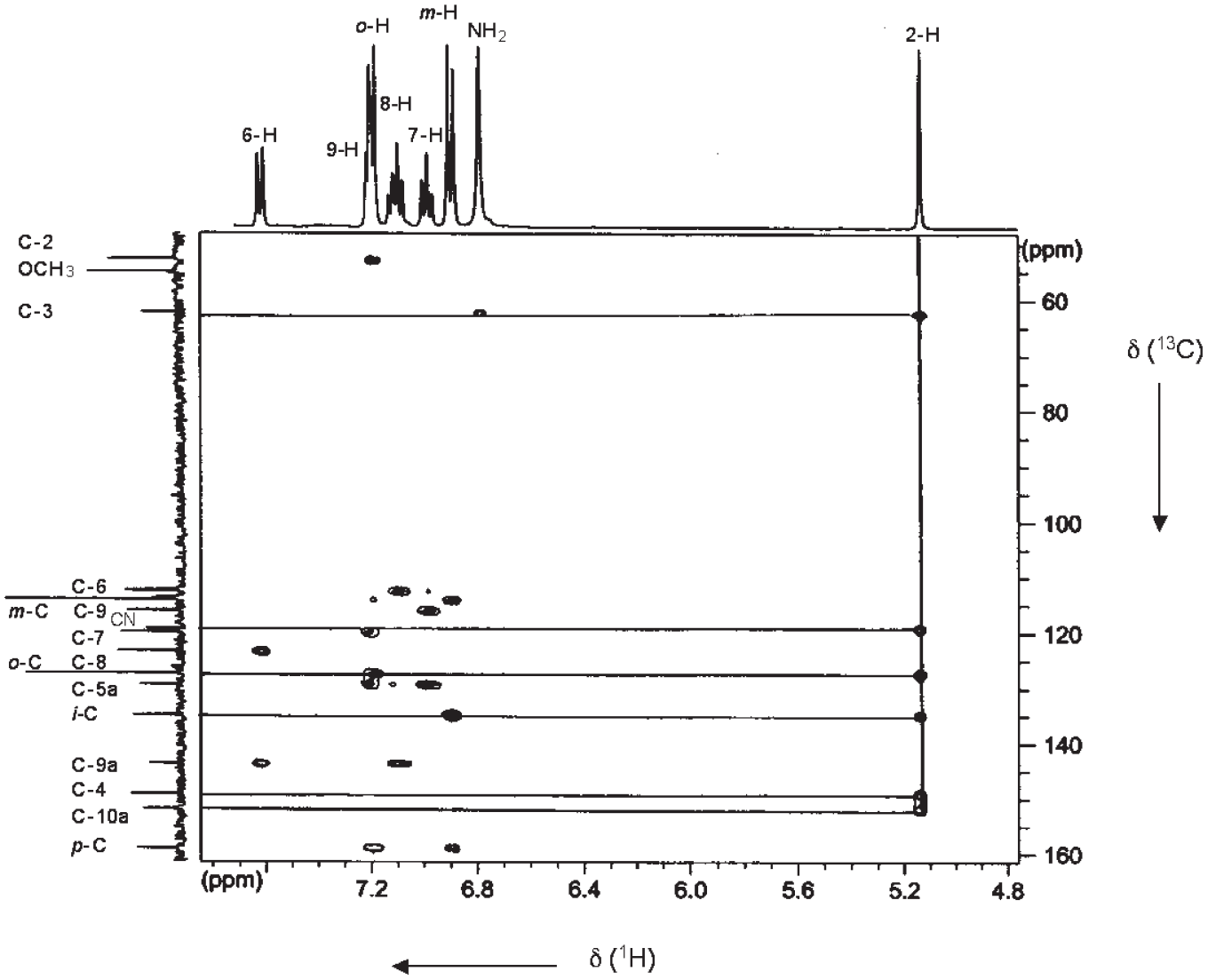
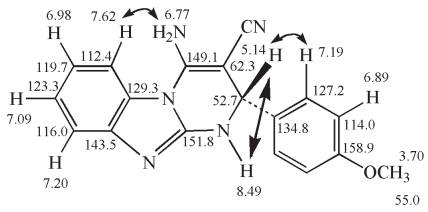



Figure 1: HMBC measurement of **14f** in $CD_3SOCD_3$. (The correlation lines indicate all $^2J$ (2-H, C) and $^3J$ (2-H, C) couplings.)

Scheme 4



cyclization with the endocyclic N atom of the azole **2** or **4**. Thus, the structures published earlier for the reaction products of **2** and **12** [6] and **4** and **12** [6,8] are not correct and the reactions of related aminoazoles [5,7] with **12** should be checked in the light of the new results.

## EXPERIMENTAL

Melting points were determined on a Kofler apparatus and are uncorrected. $^1$H and $^{13}$C NMR spectra were measured with the Bruker machines AM 400 and AMX 400 and with a Varian Mercury VX-200 spectrometer using $CD_3SOCD_3$ as solvent and TMS as internal standard. Mass spectra (EI) were recorded on a Varian CH7A (70 eV ionization energy) and FD MS on a Finnigan MAT 95.

Table 1

$^1$H NMR data of **13a - d** and **14a - c, e, f** (δ values in $CD_3SOCD_3$, TMS as internal standard).

| **13** | 2-H | 4-H | 5-H | 5-Aryl | | | 7-$NH_2$ | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *o-H* | *m-H* | *p-H* | | | | | | |
| **14** | | 1-H | 2-H | 2-Aryl | | | 4-$NH_2$ | 6-H | 7-H | 8-H | 9-H | $OCH_3$ |
| | | | | *o-H* | *m-H* | *p-H* | | | | | | |
| **13a** | 7.71 | 8.79 | 5.32 | 7.25 | ——— | 7.38 | 7.23 | | | | | |
| **13b** | 7.70 | 8.76 | 5.36 | 7.16 — | 7.36 | | 7.23 | | | | | |
| **13c** | 7.74 | 8.94 | 5.60 | 7.66 | ——— | 8.21 | 7.37 | | | | | |
| **13d** | 7.75 | 8.93 | 5.55 | 7.56 — | 8.26 | | 7.35 | | | | | |
| **14a** | | 8.61 | 5.20 | 7.24 | ——— | 7.34 | 6.84 | 7.61 | 6.99 | 7.10 | 7.22 | |
| **14b** | | 8.59 | 5.24 | 7.17 — | 7.36 | | 6.85 | 7.62 | 6.99 | 7.10 | 7.22 | |
| **14c** | | 8.77 | 5.49 | 7.62 | ——— | 8.18 | 6.98 | 7.63 | 7.00 | 7.11 | 7.24 | |
| **14e** | | 8.61 | 5.25 | 7.29 | 7.42 | | 6.86 | 7.62 | 6.98 | 7.10 | 7.22 | |
| **14f** | | 8.49 | 5.14 | 7.19 | 6.89 | | 6.77 | 7.62 | 6.98 | 7.09 | 7.20 | 3.70 |

Table 2

$^{13}$C NMR data of **13a - d** and **14a - c, e, f** (δ values in $CD_3SOCD_3$, TMS as internal standard).

| **13** | C-2 | C-3a | C-5 | 5-Aryl | | | | C-6 | 6-CN | C-7 | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | *i-C* | *o-C* | *m-C* | *p-C* | | | | | | | | | |
| **14** | | 1-H | 2-H | 2-Aryl | | | | C-3 | 3-CN | C-4 | C-5a | C-6 | C-7 | C-8 | C9 | $OCH_3$ |
| | | | | *i-C* | *o-C* | *m-C* | *p-C* | | | | | | | | | |
| **13a** | 146.8 | 151.7 | 54.0 | 143.0 | 125.9 | 128.5 | 127.8 | 56.1 | 118.8 | 153.8 | | | | | | |
| **13b**[a] | 147.0 | 151.8 | 53.3 | 139.3 | 128.2 | 115.4 | 161.7 | 55.9 | 118.8 | 153.8 | | | | | | |
| **13c** | 147.3 | 152.0 | 53.0 | 145.2 | 132.9 | 147.8 | 120.7 | 54.9 | 118.7 | 153.7 | | | | | | |
| | | | | | 123.0 | 130.5 | | | | | | | | | | |
| **13d** | 147.1 | 152.0 | 53.2 | 147.2 | 127.3 | 124.0 | 150.1 | 54.9 | 118.7 | 153.8 | | | | | | |
| **14a** | 143.6 | 151.8 | 53.2 | 142.9 | 125.9 | 128.7 | 127.8 | 62.0 | 119.2 | 149.1 | 129.3 | 112.4 | 119.9 | 123.3 | 116.1 | |
| **14b**[a] | 143.5 | 151.6 | 52.5 | 139.0 | 128.1 | 115.4 | 162.1 | 61.8 | 119.0 | 149.1 | 129.2 | 112.4 | 119.8 | 123.3 | 116.0 | |
| **14c** | 143.5 | 151.3 | 52.3 | 145.0 | 132.7 | 147.8 | 120.8 | 60.6 | 118.9 | 149.5 | 129.2 | 112.5 | 120.0 | 123.4 | 116.2 | |
| | | | | | 122.8 | 130.4 | | | | | | | | | | |
| **14e** | 143.5 | 151.5 | 52.5 | 141.7 | 127.9 | 128.6 | 132.4 | 61.5 | 119.0 | 149.2 | 129.2 | 112.3 | 119.9 | 123.3 | 116.1 | |
| **14f** | 143.5 | 151.8 | 52.7 | 134.8 | 127.2 | 114.0 | 158.9 | 62.3 | 119.1 | 149.1 | 129.3 | 112.4 | 119.7 | 123.3 | 116.0 | 55.0 |

[a] The CF coupling constants have the usual size: $^1J$ = 242 Hz, $^2J$ = 22 Hz, $^3J$ = 8 Hz, $^4J$ = 3 Hz.

## Conclusion.

Acrylonitrile (**1**) and cinnamonitriles (**9a,b**) react with aminoazoles (**2**, **4** or **6**) to linear adducts (**3**, **5**, **7**, **10**) as major products. Cyclic products as **8** and **11a,b** are at most minor components. The preferred interaction consists of an attack of an endocyclic nitrogen atom as electrophile on the β-position of the unsaturated nitrile as nucleophile. The opposite chemoselectivity is observed for the reactions of **2** or **4** with the benzylidenemalononitriles **12a - f**. In these cases the exocyclic nitrogen of the amino group attacks on the β-position of **12a - f** and a cyano group serves for the

3-(5-Amino[1.2.4]triazol-1-yl)propionitrile or 5-Amino-1-(2-cyanoethyl)-1,2,4-triazole (**3**).

Acrylonitrile (**1**, 0.35 g, 6.5 mmol) and 3-amino-1,2,4-triazole (**2**, 0.42 g, 5.0 mmol) were refluxed in a mixture of 30 % dimethylamine in ethanol for 2 h. The volatile parts were evaporated and the residue triturated with 3 mL acetonitrile. Filtration and recrystallization from acetonitrile yielded 0.07 g (10 %) of **3**

which melted at 136 - 138 °C. $^1$H NMR ($CD_3SOCD_3$): δ = 2.97 (t, $^3J$ = 6.4 Hz, 2 H, β-$CH_2$), 4.18 (t, $^3J$ = 6.4 Hz, 2 H, α-$CH_2$), 5.36 (s, 2 H, $NH_2$), 8.01 (s, 1 H, 4-H); $^{13}$C NMR ($CD_3SOCD_3$): δ = 18.1 (β-$CH_2$), 43.7 (α-$CH_2$), 118.3 (CN), 143.0 (HC-3), 164.4 (C-5). EI MS: *m/z* (%) = 137 (52, $M^+$), 97 (88), 70 (100).

*Anal.* Calcd. for $C_5H_7N_5$ (137.1): C, 43.79; H, 5.14; N, 51.07. Found: C, 43.56; H, 5.03; N, 50.85.

3-(2-Aminobenzimidazol-1-yl)propionitrile or 5-amino-1-(2-cyanoethyl)benzimidazole (**5**).

The procedure described above for **3** yielded from 0.35 g (6.5 mmol) **1** and 0.67 g (5.0 mmol) **4** 0.33 g (35 %) of **5** which melted at 174 – 176 °C (recrystallization from $CHCl_3$). $^1$H NMR ($CD_3SOCD_3$): δ = 2.89 (t, $^3J$ = 6.8 Hz, 2 H, β-$CH_2$), 4.30 (t, $^3J$ = 6.8 Hz, 2 H, α-$CH_2$), 6.54 (s, 2 H, $NH_2$), 6.91 (m, 2 H, 5-H, 6-H), 7.12, m, 1 H / 7.26, m, 1 H (4-H, 7-H). $^{13}$C NMR ($CD_3SOCD_3$): δ = 17.0 (β-$CH_2$), 37.2 (α-$CH_2$), 107.7, 114.7, 118.1, 120.6 (C-4, C-5, C-6, C-7), 118.5 (CN), 133.7, 142.7 (C-3a, C-7a), 154.4 (C-2). EI MS: *m/z* (%) = 186 (84, $M^+$), 146 (63), 133 (49), 119 (27), 91 (100).

*Anal.* Calcd. for $C_{10}H_{10}N_4$ (186.2): C, 64.50; H, 5.41; N 30.09. Found: C, 64.21; H, 5.18; N, 29.81.

3-(5-Amino-3-methylpyrazol-1-yl)propionitrile or 5-Amino-1-(2-cyanoethyl)-3-methylpyrazole (**7**).

A mixture of 265 mg (5.0 mmol) **1** and 485 mg (5.0 mmol) **6** [14] in 7.5 mL pyridine/15 mL $H_2O$ was refluxed for 12 h. The volatile parts were evaporated *in vacuo* and the residue triturated with ethanol. The raw product was collected by filtration and washed with ethanol and acetonitrile. Recrystallization from ethyl acetate yielded 280 mg (37 %) of pure **7** which melted at 94 – 96 °C. $^1$H NMR ($CD_3SOCD_3$): δ = 2.13, (s, 3 H, $CH_3$), 2.83 (t, $^3J$ = 6.8 Hz, 2 H, β-$CH_2$), 3.57 (s, 2 H, $NH_2$), 4.18 (t, $^3J$ = 6.8 Hz, 2 H, α-$CH_2$), 5.40 (s, 1 H, 4-H); $^{13}$C NMR ($CD_3SOCD_3$): δ = 13.9 ($CH_3$), 18.7 (β-$CH_2$), 42.5 (α-$CH_2$), 92.9 (C-4), 118.1 (CN), 145.1, 148.9 (C-3, C-5). EI MS: *m/z* (%) = 150 (31, $M^+$), 98 (100).

*Anal.* Calcd. for $C_7H_{10}N_4$ (150.2): C, 55.98; H, 6.71; N, 37.31. Found: C, 55.65; H, 6.39; N, 37.10.

The raw product contained a second component **8** which showed in the $^1$H NMR spectrum in $CD_3SOCD_3$ signals at δ = 2.19 (s, 3 H, $CH_3$), 2.81 (t, $^3J$ = 6.3 Hz, 2 H, $CH_2$), 3.49 (s, 2 H, $NH_2$), 4.09 (t, $^3J$ = 6.3 Hz, 2 H, $CH_2$), 5.40 (s, 1 H, CH). Signal integration gave a ratio **7**:**8** = 3:1.

3-(2-Aminobenzimidazol-1-yl)-3-phenylpropionic Acid Benzimidazol-2-ylamidine (**10a**) and 3-(Benzimidazol-2-ylamino)-1-phenyl-1,2-dihydropyrimido[1,2-*a*]benzimidazole (**11a**).

A mixture of 0.39 (3.0 mmol) cinnamonitrile (**9a**) and 0.40 g (3.0 mmol) **4** was refluxed in 0.4 mL DMF for 15 min, diluted with 10 mL ethyl acetate and chromatographed on neutral $Al_2O_3$ (20 x 3 cm). The first fraction obtained with ethyl acetate as eluent consisted of small amounts of unreacted **4** and **9a**. A 4:1 mixture of ethylacetate and methanol gave then 110 mg (19 %) of **10a** and 20 mg (4 %) of **11a**. Compound **10a** decomposes at 230 °C and compound **11a** does not melt below 310 °C.

**10a**: $^1$H NMR ($CD_3SOCD_3$): δ = 3.15 (dd, $^2J$ = 16.4 Hz, $^3J$ = 3.5 Hz, 1 H, 2-H), 3.50 (dd, $^2J$ = 16.4 Hz, $^3J$ = 7.6 Hz, 1 H, 2-H), 6.01 (dd, $^3J$ = 3.5 Hz, $^3J$ = 7.6 Hz, 1 H, 3-H), 7.10 (m, 1 H, aromat. H), 7.12 – 7.21 (m, 5 H, aromat. H), 7.24 (m, 1 H, aromat. H), 7.31 – 7.40 (m, 5 H, aromat. H), 7.48 (m, 1 H, aromat. H), 8.40 (br. s, 3 H, $NH_2$, NH), 9.10 (br. s, 1 H, NH), 9.30 (br. s, 1 H, NH); $^{13}$C NMR ($CD_3SOCD_3$): δ = 32.2 ($CH_2$), 51.5 (CH), 110.1, 111.3, 111.3, 113.0, 122.4, 122.4, 122.9, 123.4 (CH, benzimidazole) 125.8, 128.5, 129.1 (CH, phenyl), 129.7, 130.2, 131.2, 138.1 (aromat. $C_q$), 150.9, 152.4 ($C_q$, imidazole), 168.2 ($C_q$, amidine). EI MS: *m/z* (%) = 262 (100, [$M^+$ - 133]), 133 (56, [$M^+$ - 262]) [15].

*Anal.* Calcd. for $C_{23}H_{21}N_7$ (395.5): C, 69.85; H, 5.35; N, 24.79. Found: C, 69.53; H, 5.47; N, 24.55.

**11a**: $^1$H NMR ($CD_3SOCD_3$): δ = 3.16 (dd, $^2J$ = 16.6 Hz, $^3J$ = 2.4 Hz, 1 H, 2-H), 3.72 (dd, $^2J$ = 16.6 Hz, $^3J$ = 7.3 Hz, 1 H, 2-H), 6.00 (dd, $^3J$ = 2.4 Hz, $^3J$ = 7.3 Hz, 1 H, 1-H), 6.95 – 7.20 (m, 7 H, aromat. H), 7.21 – 7.39 (m, 3 H, aromat. H), 7.42 – 7.58 (m, 3 H, aromat. H), 12.50 (br. s, 2 H, 2 NH); $^{13}$C NMR ($CD_3SOCD_3$): δ = 35.6 ($CH_2$), 51.9 (CH), 109.3, 114.0, 114.0, 117.7, 121.1, 121.6, 121.6, 125.4, 125.7, 128.2, 129.0 (aromat. CH), 132.5, 135.7, 139.3, 142.1 (aromat. $C_q$), 148.8, 151.4, 157.7 ($C_qN_x$, x = 2,3). EI MS: *m/z* (%) = 378 (79, $M^+$), 301 (100), 189 (25).

*Anal.* Calcd. for $C_{23}H_{18}N_6$ (378.4): C, 73.00; H, 4.79; N, 22.21. Found: C, 72.65; H, 4.42; N, 21.95.

3-(2-Aminobenzimidazol-1-yl)-3-(4-chlorophenyl)propionic Acid Benzimidazol-2-ylamidine (**10b**) and 3-(Benzimidazol-2-ylamino)-1-(4-chlorophenyl)-1,2-dihydropyrimido[1,2-*a*]-benzimidazole (**11b**).

The preparation according to the procedure described for **10a** and **11a** yielded 0.33 g (51 %) **10b** 0.07 g (11 %) of **11b** from 0.40 g (3.0 mmol) of **4** and 0.49 g (3.0 mmol) of 4-chlorocinnamonitrile (**9b**). The crystals of **10b** decompose at 215 °C; **11b** does not melt below 310 °C.

**10b**: $^1$H NMR ($CD_3SOCD_3$): δ = 3.10 (dd, $^2J$ = 16.4 Hz, $^3J$ = 3.1 Hz, 1 H, 2-H), 3.46 (dd, $^2J$ = 16.4 Hz, $^3J$ = 7.8 Hz, 1 H, 2-H), 6.01 (dd, $^3J$ = 7.8 Hz, $^3J$ =3.1 Hz, 1 H, 3-H), 7.09 – 7.16 (m, 4 H, aromat. H), 7.19 (m, 2 H, aromat. H), 7.21 (m, 1 H, aromat. H), 7.31 – 7.37 (m, 2 H, aromat. H), 7.43 (m, 2 H, aromat. H), 7.47 (m, 1 H, aromat. H), 8.34 (br. s, 3 H, $NH_2$, NH), 8.88 (br. s, 1 H, NH), 9.03 (br. s, 1 H, NH); $^{13}$C NMR ($CD_3SOCD_3$): δ = 32.2 ($CH_2$), 50.8 (CH), 109.8, 111.3, 111.3, 113.6, 122.3, 122.3, 122.5, 123.1 (CH, benzimidazole), 127.8, 129.1 (CH, aryl), 130.0, 130.6, 132.9, 133.1, 137.4 (aromat. $C_q$), 151.1, 152.7 ($C_q$, imidazole), 167.5 ($C_q$, amidine). EI MS: *m/z* (%) = 296 (10, [$M^+$ - 133]), 133 (100, [$M^+$ - 296]) [15].

*Anal.* Calcd. for $C_{23}H_{20}ClN_7$ (429.9): C, 64.26; H, 4.69; N, 22.81. Found: C, 64.29; H, 4.75; N, 22.58.

**11b**: $^1$H NMR ($CD_3SOCD_3$): δ = 3.15 (dd, $^2J$ = 16.1 Hz, $^3J$ = 2.7 Hz, 1 H, 2-H), 3.73 (dd, $^2J$ = 16.1 Hz, $^3J$ = 7.2 Hz, 1 H, 2-H), 6.03 (dd, $^3J$ = 7.2 Hz, $^3J$ = 2.7 Hz, 1 H, 1-H), 7.03 – 7.19 (m, 7 H, aromat. H), 7.40 (m, 2 H, aromat. H), 7.48 – 7.55 (m, 3 H, aromat. H), 12.6 (br. s, 2 H, NH); $^{13}$C NMR ($CD_3SOCD_3$): δ = 35.5 ($CH_2$), 51.3 (CH), 109.3, 113.9, 113.9, 117.6, 121.3, 121.7, 121.7, 127.7, 128.2, 129.0 (aromat. CH), 132.3, 132.8, 135.5, 138.3, 141.8 (aromat. $C_q$), 148.9, 151.2 ($C_q$, imidazole), 167.9 ($C_q$, amidine). EI MS: *m/z* (%) = 412 (74, $M^+$), 301 (100).

*Anal.* Calcd. for $C_{23}H_{17}ClN_6$ (412.9): C, 66.91; H, 4.15; N, 20.35. Found: C, 66.68; H, 3.94; N, 20.04.

General Procedure for the Preparation of the 7-Amino-5-aryl-4,5-dihydro-(1,2,4)-triazolo[1,5-*a*]pyrimidine-6-carbonitriles (**13a-d**).

A mixture of 0.17 g (2.0 mmol) **2** and 2.0 mmol of malonodinitrile **12a-d** was refluxed in 2 mL 30 % dimethylamine in ethanol for 5 min. The precipitate formed after cooling was collected by filtration and recrystallized from ethanol.

7-Amino-4,5-dihydro-5-phenyl-(1,2,4)-triazolo[1,5-*a*]pyrimidine-6-carbonitrile (**13a**).

This compound was obtained in 70 % yield, mp 267 – 269 °C. EI MS: *m/z* (%) = 238 (31, $M^+$), 161 (100).

*Anal.* Calcd. for $C_{12}H_{10}N_6$ (238.3): C, 60.50; H, 4.23; N, 35.27. Found: C, 60.38; H, 4.07; N, 35.13.

7-Amino-5-(4-fluorophenyl)-4,5-dihydro-(1,2,4)-triazolo[1,5-*a*]-pyrimidine-6-carbonitrile (**13b**).

This compound was obtained in 27 % yield, mp 255 – 256 °C. FD MS: *m/z* (%) = 257 (100, $[M + 1]^+$).

*Anal.* Calcd. for $C_{12}H_9FN_6$ (256.2): C, 56.25; H, 3.54; N, 32.80. Found: C, 56.18; H, 3.49: N, 32.59.

7-Amino-4,5-dihydro-5-(3-nitrophenyl)-(1,2,4)-triazolo[1,5-*a*]-pyrimidine-6-carbonitrile (**13c**).

This compound was obtained in 42 % yield, mp 258 – 259 °C. FD MS: *m/z* (%) = 284 (100, $[M + 1]^+$).

*Anal.* Calcd. for $C_{12}H_9N_7O_2$ (283.3): C, 50.88; H, 3.20; N, 34.62. Found C, 50.99; H, 3.06; N, 34.67.

7-Amino-4,5-dihydro-5-(4-nitrophenyl)-(1,2,4)-triazolo[1,5-*a*]-pyrimidine-6-carbonitrile (**13d**).

This compound was obtained in 26 % yield, mp 275 (decomp.). FD MS *m/z* (%) = 284 (100, $[M + 1]^+$).

*Anal.* Calcd. for $C_{12}H_9N_7O_2$ (283.3): C, 50.88; H, 3.20; N, 34.62. Found: C, 51.05; H, 3.33; N, 34.85.

General Procedure for the Preparation of the 4-Amino-2-aryl-1,2-dihydro-pyrimido[1,2-*a*]benzimidazole-3-carbonitriles (**14a-c,e,f**).

A mixture of 266 mg (2.0 mmol) **4** and 2.0 mmol of malonodinitrile **12a-c,e,f** was refluxed in 2 mL 30 % dimethylamine in ethanol for 5 min. The precipitate formed after cooling was collected by filtration and recrystallized from ethanol.

4-Amino-1,2-dihydro-2-phenylpyrimido[1,2-*a*]benzimidazole-3-carbonitrile (**14a**).

This compound was obtained in 45 % yield, mp 205 – 207 °C, lit. [13] 218 °C. EI MS: *m/z* (%) = 287 (42, $M^+$), 210 (66), 133 (100).

*Anal.* Calcd. for $C_{17}H_{13}N_5$ (287.3): C, 71.06; H, 4.56; N, 24.37. Found: C, 71.86; H, 4.46; N, 24.29.

4-Amino-2-(4-fluorophenyl)-1,2-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrile (**14b**).

This compound was obtained in 46 % yield, mp 232 (decomp.) FD MS: *m/z* (%) = 306 (100, $[M + 1]^+$).

*Anal.* Calcd. for $C_{17}H_{12}FN_5$ (305.3): C, 66.88; H, 3.96; N, 22.94. Found: C, 66.71; H, 3.73; N 22.86.

4-Amino-1,2-dihydro-2-(3-nitrophenyl)pyrimido[1,2-*a*]benzimidazole-3-carbonitrile (**14c**).

This compound was obtained in 37 % yield, 216 – 217 °C. FD MS: *m/z* (%) = 333 (100, $[M + 1]^+$).

*Anal.* Calcd. for $C_{17}H_{12}N_6O_2$ (332.3): C, 61.44; H, 3.64; N, 25.29. Found: C, 61.27; H, 3.50; N 25.22.

4-Amino-2-(4-chlorophenyl)-1,2-dihydropyrimido[1,2-*a*]benzimidazole-3-carbonitrile (**14d**).

This compound was obtained in 37 % yield, mp 232 (decomp.), lit. 238 °C [13]. FD MS: *m/z* (%) = 322 (100, $[M + 1]^+$).

*Anal.* Calcd. for $C_{17}H_{12}ClN_5$ (321.8): C, 63.46; H, 3.76; N, 21.77. Found: C, 63.25; H, 3.62; N, 21.71.

4-Amino-1,2-dihydro-2-(4-methoxyphenyl)pyrimido[1,2-*a*]benzimidazole-3-carbonitrile (**14f**).

This compound was obtained in 30 % yield, mp 212 – 213 °C, lit. [13] 197 °C. FD MS: *m/z* (%) = 318 (100, $[M + 1]^+$).

*Anal.* Calcd. for $C_{18}H_{15}N_5O$ (317.4): C, 68.13; H, 4.76; N, 22.07. Found: C, 67.82; H, 4.55; N, 21.91.

Acknowledgements.

We are grateful to the German Academic Exchange Service (DAAD) for a grant.

REFERENCES AND NOTES

[1a] Y. Tsuda, T. Mishina, M. Obata, K. Araki, J. Inui, T. Nakamura, (to Yoshitomi Pharmaceutical Industries, Ltd.), *U.S. Patent* 4,918,074 (1990); *Chem. Abstr.* **114**, 81873 (1991); [b] N. Tsuda, T. Mishina, M. Obata, K. Araki, A. Inui, T. Nakamura, (to Yoshitomi Pharmaceutical Industries, Ltd.), *Jap. Patent* 63,101,383 (1988); *Chem. Abstr.* **109**, 128988 (1988); [c] Y. Tsuda, T. Mishina, M. Obata, K. Araki, J. Inui, T. Nakamura, (to Yoshitomi Pharmaceutical Industries, Ltd.), *Eur. Patent* 0,328,700 (1989); *Chem. Abstr.* **113**, 29258 (1990); [d] S. M. Desenko, V. D. Orlov, V. V. Lipson, N. I. Gorbenko, L. P. Pivovarevich, E. N. Ryndina, V. V. Moroz, V. P. Varavin, *Khim-Farm. Zh.* **29**, 37-38 (1995); *Chem. Abstr.* **124**, 239 (1996); [e] K. S. Atwal, S. Moreland, *Bioorg. Med. Chem. Lett.* **1**, 291-294 (1991).

[2] S. M. Desenko, *Khim. Geterotsikl. Soedin.* 147-159 (1995); *Chem. Heterocycl. Compd. (Engl. Transl.)* **31**, 125-136 (1995).

[3] See for example A. N. Kost, Y. V. Konnova, V. V. Ershov, E. G. Rukhadze, *Zh. Obshch. Khim.* **29**, 498-502 (1959); *Engl. Edition: J. Gen. Chem. USSR* **29**, 496-499 (1959).

[4a] S. M. Desenko, S. A. Komykhov, V. D. Orlov, H. Meier, *J. Heterocyclic Chem.* **35**, 989-990 (1998); [b] S. A. Komykhov, S. Desenko, A. S. Kaganovsky, V. D. Orlov, H. Meier, *J. Heterocyclic Chem.* **37**, 195-196 (2000).

[5a] M. H. Elnagdi, A. H. H. Elghandour, M. K. A. Ibrahim, I. S. A. Hafiz, *Z. Naturforsch.* **47b**, 572-578 (1992); [b] M. H. Elnagdi, K. U. Sadek, F. M. A. Galil, S. M. E. Hassan, *Arch. Pharm.* **321**, 851-854 (1988); [c] H. A. Elfahham, F. M. Abdel-Galil, Y. R. Ibraheim, M. H. Elnagdi, *J. Heterocycl. Chem.* **20**, 667-670 (1983).

[6] M. K. A. Ibrahim, *Indian. J. Chem.* **27B**, 478-481 (1988); *Chem. Abstr.* **110,** 57610 (1988).

[7] G. E. H. Elgemeie, B. Y. Riad, G. A. M. Nawwar, S. Elgamal, *Arch. Pharm.* **320**, 223-228 (1987).

[8] A. O. Abdelhamid, B. Y. Riad, S. I. Aziz, *Arch. Pharm.* **320**, 642-646 (1987).

[9a] M. H. Elnagdi, S. M. Fahmy, M. R. H. Elmoghayar, M. A. M. Iliaz, *Z. Naturforsch.* **30b**, 778-783 (1975); [b] M. H. Elnagdi, D. H. Fleita, M. R. H. Elmoghayar, *Tetrahedron* **31**, 63-67 (1975).

[10] See also V. D. Orlov, S. M. Desenko, K. A. Potekhin, Y. T. Struchkov, *Chem. Heterocycl. Compd. (Engl. Transl.)* **24**, 192-196 (1988).

[11] See also S. M. Desenko, V. D. Orlov, *Chem. Heterocycl. Compd. (Engl. Transl.)* **25**, 894-898 (1989).

[12] See also V. D. Orlov, J. Quiroga, N. N. Kolos, S. M. Desenko, *Chem. Heterocycl. Compd. (Engl. Transl.)* **24**, 791-794 (1988).

[13] B. Insuasty, A. Salcedo, R. Abonia, J. Quiroga, M. Nogueras, A. Sanchez, *Heterocycl. Commun.* **8** 287-292 (2002).

[14] N. L. Nam, I. I. Grandberg, V. I. Sorokin, *Chem. Heterocycl. Compd. (Engl. Transl.)*, **36**, 281-283 (2000); *Khim. Geterotsikl. Soedin.*, **36**, 342-344 (2000).

[15] Cleavage of **10a,b** by elimination of 2-aminobenzimidazole (**4**) [*m/z* = 133].