Transformations of Heterocyclic Amidines and Amide Oximes: Synthesis of *s*-Triazolo[1′,5′:1,6]pyrimido[4,5-*c*]pyridazines, *s*-Triazolo[1′,5′:2,3]pyridazino[4,5-*c*]quinoline and 7*H*-2,3,4,6,7-Pentaazabenz[*d*,*e*]anthracene, Derivatives of Novel Heterocyclic Systems

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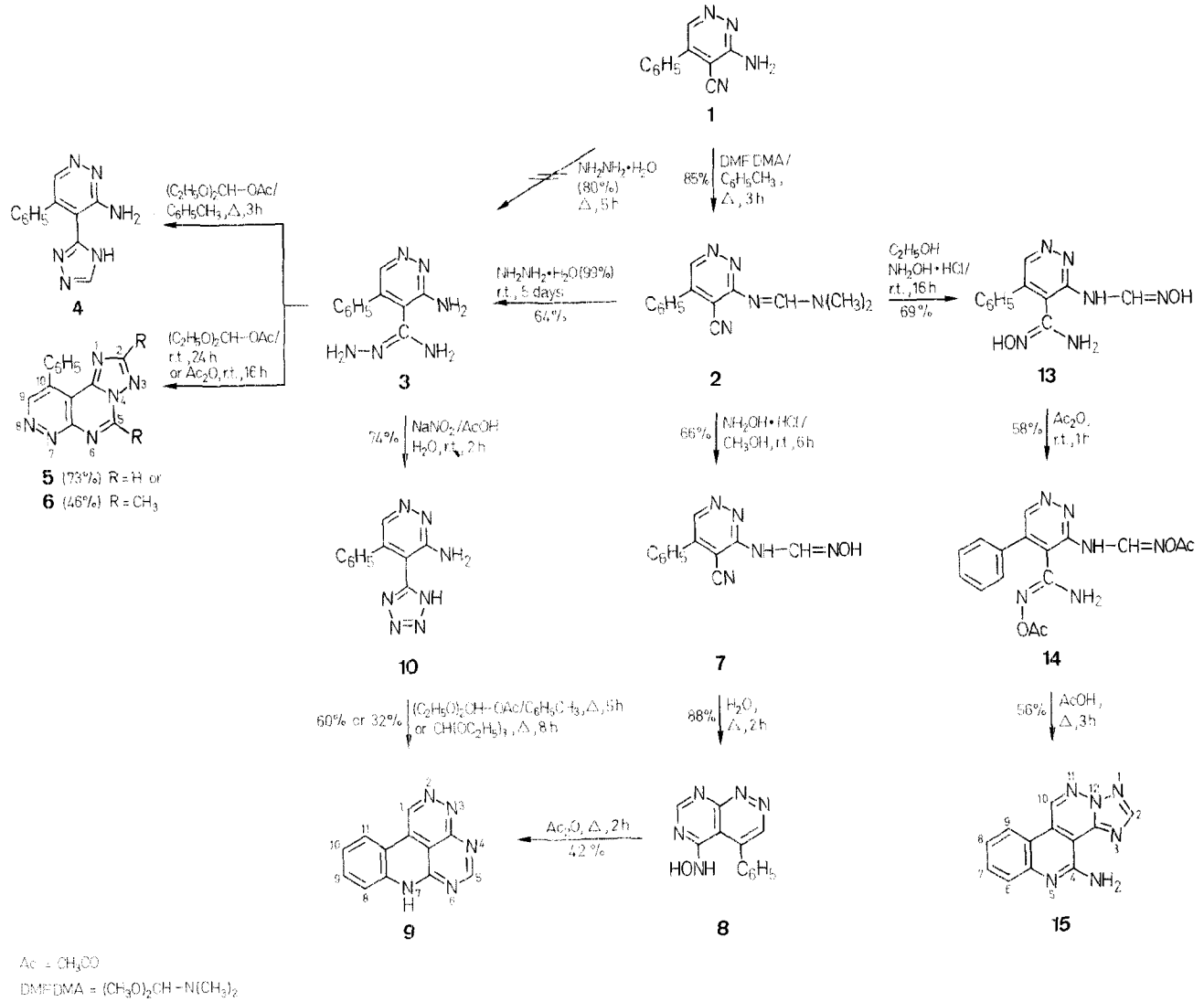
3-Amino-4-cyano-5-phenylpyridazine (**1**) is transformed into the corresponding amidine **2**, carboxamidrazone **3** and formamide oximes **7** and **13**. These intermediates are cyclized to three novel heterocyclic systems: *s*-triazolo[1′,5′:1,6]pyrimido[4,5-*c*]pyridazines **5** and **6**, *s*-triazolo[1′,5′:2,3]pyridazino[4,5-*c*]quinoline (**15**), and 7*H*-2,3,4,6,7-pentaazabenz[*d*,*e*]anthracene (**9**).

Heterocyclic compounds with a formamidine, formamide oxime and/or carboxamide oxime functional groups are versatile synthons for the preparation of various heterocyclic bicyclic systems[1–4]. When a suitable group, such as ring nitrogen atom, amino, cyano, hydroxy or potential hydroxy, mercapto or potential mercapto or other groups, is attached at the *ortho* position to the formamidine, formamide oxime or carboxamidoxime group, the cyclization takes place readily to give the corresponding azoloazines with a bridgehead nitrogen atom, fused imidazoles, oxazoles, triazoles, isothiazoles, pyrimidines, etc.[5–7].

As an extension of these studies we report here a new cyclization reaction with participation of the phenyl group at the *ortho* position with respect to the carboxamide oxime group.

3-Amino-4-cyano-5-phenylpyridazine (**1**)[8] was converted to the amidine **2** by treatment with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA). When **2** was left in the presence of hydrazine hydrate (99%) at room temperature, hydrazine was added to the cyano group followed by hydrolysis of the amidine group to form the amidrazone **3**. On the other hand, the same compound **3** could not be prepared directly from **1** and hydrazine hydrate (80%) even under refluxing conditions. The cyclization of **3** with diethoxymethyl acetate (DEMA) in toluene at reflux temperature gave the corresponding triazolyl substituted pyridazine derivative **4**. However, when a mixture of **3** and DEMA was



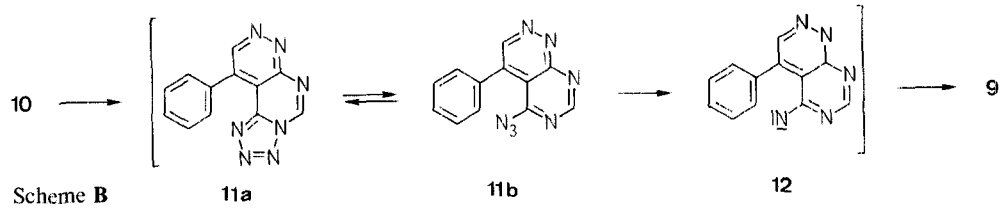
Scheme A

left at room temperature, further cyclization, in which the amino group at position 3 of the pyridazine ring and NH group of the triazolyl system are involved, occured to give a derivative **5** of the novel triazolo[1′,5′: 1,6]pyrimido[4,5-*c*]pyridazine system. When acetic anhydride was employed instead of diethoxymethyl acetate the corresponding methyl substituted derivative **6** was isolated (Scheme **A**).

When **2** was treated with hydroxyamine hydrochloride in methanol at room temperature, the formamidine group was converted into the corresponding formamide oxime to give the compound **7**. By boiling **7** in water, cyclization between formamide oxime group and the adjacent cyano group took place to afford pyrimido[4,5-*c*]pyridazine derivative **8**. This cyclization represents a new alternative method of preparation of pyrimido[4,5-*c*]pyridazines in comparison to the previously reported syntheses[9,10]. On the other hand, by heating **8** in acetic anhydride cyclodehydration involving the participation of the adjacent phenyl group occurred to give the tetracyclic 7*H*-2,3,4,6,7-pentaazabenz[*d*,*e*]anthracene (**9**). Compound **9** was also prepared from the amidrazone **3**, by first converting it into the tetrazolyl substituted pyridazine **10** with nitrous acid, followed by reaction with triethyl orthoformate (Scheme **A**).

This latter transformation can be explained in the following way. The compound **10** cyclizes with triethyl orthoformate to the phenyl substituted tetrazolylpyrimidopyridazine derivative **11a**, which is in equilibrium with the azido form **11b**. This decomposes thermally into the nitrene **12** followed by insertion into the C—H bond of the adjacent phenyl group to give the tetracycle **9**. (Scheme **B**).

The structure was established on the basis of its analytical and spectral data. The ^{1}H-NMR spectrum of **9** shows two singlets at δ = 9.83 ppm for 1-H and δ = 8.33 ppm for 5-H and two multiplets at δ = 7.3–7.8 ppm for 8-H, 9-H and 10-



Scheme **B**

H and at δ = 8.35–8.50 ppm for 11-H integrating for four protons. This strongly indicates that cyclization of the hydroxyamino group of the compound **8** or the intramolecular insertion of the nitrene group of the intermediate **11b**, must have taken place to the adjacent phenyl group to form the tetracyclic compound **9**.

On the other hand, when the amidine **2** was treated with hydroxylamine at room temperature, the formamidine group was transformed into the formamide oxime and at the *same time addition to cyano group also took place to give the* corresponding carboxamide oxime derivative **13**. This was acetylated with acetic anhydride to form the diacetyl *derivative* **14**. *In boiling acetic acid, the O-acetylated* formamide oxime group cyclized, involving the adjacent pyridazine nitrogen atom, into fused triazolo derivative in an *analogous manner as described earlier for other O-acetylated* *N*-heteroarylformamide oximes, while *O*-acetylated carboxamidoxime group cyclized to the adjacent phenyl group to yield tetracyclic *4-amino-s-triazolo[1',5':2,3]pyrid*azino[4,5-*c*] quinoline **(15)**.

The structure of **15** is established based on analytical and spectral data. The ^{1}H-NMR spectrum shows two singlets at δ = 10.50 ppm for 1-H and at δ = 9.55 ppm for 5-H, and a multiplet at δ = 1.40–1.50 ppm for H-9 to H-12 integrating for four protons. This suggests the cyclization of the *O*-acetylated formamide oxime group to the pyridazine ring and cyclization of the *O*-acetylated carboxamidoxime group to the phenyl ring to give the compound **15**.

3-Amino-4-cyano-5-phenylpyridazine **(1)** was prepared in essentially the same way as reported in the literature.[8]

4-Cyano-3-(*N,N*-dimethylaminomethyleneamino-5-phenylpyridazine (2):

Method A: A mixture of 3-amino-4-cyano-5-phenylpyridazine (1[8]; 588 mg, 3 mmol) and *N,N*-dimethylformamide dimethyl acetal (310 mg, 3 mmol) in toluene (3 ml) is heated under reflux for 3 h, cooled and the solid formed is collected by suction; yield: 653 mg (85%); m.p. 165–168°C (toluene).

$C_{14}H_{13}N_5$	calc.	C 66.91	H 5.21	N 27.87
(251.3)	found	67.09	5.35	27.60

^{1}H-NMR (CDCl$_3$/TMS): δ = 3.12, 3.22 (2 s, 3 H each, CH$_3$); 7.35–7.85 (m, 5 H$_{arom}$); 8.78 (s, 1 H, N=CH); 9.00 ppm (s, 1 H, 6-H).

Method B: A mixture of 3-amino-4-cyano-5-phenylpyridazine (**1**[8]; 196 mg, 1 mmol), phosphorus oxychloride (2 ml) and dimethylformamide (4 ml) is left at room temperature for 12 h. The reaction mixture is poured into crushed ice (8 g) and neutralized with concentrated aqueous solution of ammonia. The precipitate is collected by suction, dried and recrystallized from ethanol to give **2**; yield: 130 mg (52%); m.p. 165–168°C.

3-Amino-5-phenylpyridazine-4-carboxamidrazone (3):

A mixture of 4-cyano-3-(*N,N*-dimethylaminomethyleneamino)-5-phenylpyridazine (**2**; 251 mg, 1 mmol) and hydrazine hydrate (99%, 3 ml) is left for 5 days at room temperature. The precipitate formed is collected by suction; yield: 146 mg (64%); m.p. 196–198°C (ethanol).

$C_{11}H_{12}N_6$	calc.	C 57.88	H 5.30	N 36.82
(228.2)	found	57.75	5.45	36.99

^{1}H-NMR (DMSO-d_6/TMS): δ = 5.1–5.65 (br s, 3 H, NH, NH$_2$); 6.14 (br s, 3 H, NH, NH$_2$); 7.38 (m, 5 H$_{arom}$); 8.41 ppm (s, 1 H, 6-H).

MS (70 eV): *m/e* = 228 (M$^+$).

3-Amino-5-phenyl-4-(4*H*-1,2,4-triazol-3-yl)-pyridazine (4):

A mixture of 3-amino-5-phenylpyridazine-4-carboxamidrazone (**3**; 228 mg, 1 mmol) and diethoxymethyl acetate (162 mg, 1 mmol) in toluene (3 ml) is heated under reflux for 3 h and left in the refrigerator for 12 h. The precipitated solid is collected by suction; yield: 190 mg (80%); m.p. 317–320°C (ethanol).

$C_{12}H_{10}N_6$	calc.	C 60.49	H 4.23	N 35.27
(238.2)	found	60.17	4.13	35.15

^{1}H-NMR (DMSO-d_6/TMS): δ = 6.65 (br s, 3 H, NH, NH$_2$); 7.05–7.50 (m, 5 H$_{arom}$); 8.54 (s, 1 H, 5-H); 8.52 ppm (s, 1 H, 6-H).

MS (70 eV): *m/e* = 238 (M$^+$).

10-Phenyl-1,2,4-triazolo[1',5':1,6]pyrimido[4,5-*c*]pyridazine (5):

A mixture of 3-amino-5-phenylpyridazine-4-carboxamidrazone (**3**; 228 mg, 1 mmol) and diethoxymethyl acetate (2 ml) is left for 24 h at room temperature. The precipitate formed is collected by suction; yield: 181 mg (73%); m.p. 317–320°C (methanol/dimethylformamide).

$C_{13}H_8N_6$	calc.	C 62.90	H 3.25	N 33.85
(248.2)	found	62.64	3.53	33.76

^{1}H-NMR (DMSO-d_6/TMS): δ = 7.75–7.94 (m, 5 H$_{arom}$); 8.55 (s, 1 H, 5-H); 9.46 (s, 1 H, 9-H); 9.88 ppm (s, 1 H, 3 H).

2,5-Dimethyl-10-phenyl-1,2,4-triazolo[1',5':1,6]pyrimido[4,5-*c*]pyridazine (6):

Method A: A mixture of 2-amino-5-phenylpyridazine-4-carboxamidrazone (**3**; 228 mg, 1 mmol) and acetic anhydride (2 ml) is left for 16 h at room temperature. The volatile components are evaporated *in vacuo*, water (4 ml) and ethanol (4 ml) are added to the residue, the solid formed is collected by suction; yield: 121 mg (46%); m.p. 153–155°C (ethanol/water).

$C_{15}H_{10}N_6$	calc.	C 65.20	H 4.38	N 30.42
(276.3)	found	65.40	4.26	30.68

^{1}H-NMR (CDCl$_3$/TMS): δ = 2.55 (s, 3 H, 3-CH$_3$); 3.13 (s, 3 H, 5-CH$_3$); 7.55 (m, 5 H$_{arom}$); 9.36 ppm (s, 1 H, 9-H).

MS (70 eV): *m/e* = 276 (M$^+$).

Method B: A mixture of 3-amino-5-phenylpyridazine-4-carboxamidrazone (**3**; 114 mg, 0.5 mmol) and triethyl orthoacetate (1.5 ml) is heated under reflux for 4 h. After standing in refrigerator for 24 h, the precipitate formed is collected by suction and recrystallized from a mixture of ethanol and water; yield: 86 mg (62%).

4-Cyano-3-hydroxyiminomethyleneamino-5-phenylpyridazine (7):

To a suspension of 4-cyano-3-(*N,N*-dimethylaminomethyleneamino)-5-phenylpyridazine (**2**; 251 mg, 1 mmol) in methanol (5 ml), hydroxylamine hydrochloride (105 mg, 1.5 mmol) is added. The mixture is stirred at room temperature for 6 h. The precipitate formed is collected by suction and washed with methanol; yield: 158 mg (66%); m.p. 170–175°C.

$C_{12}H_9N_5O$	calc.	C 60.24	H 3.79	N 29.29
(239.2)	found	59.88	3.75	28.91

^{1}H-NMR (DMSO-d_6/TMS): δ = 7.35–7.95 (m, 5 H$_{arom}$); 8.05 (d, 1 H, *J* = 9.3 Hz, CHNH); 8.55 (d, 1 H, *J* = 9.3 Hz, CHNH); 9.13 (s, 1 H, 6-H); 9.05 ppm (br s, 1 H, OH).

MS (70 eV): *m/e* = 239 (M$^+$).

5-Hydroxyimino-4-phenylpyrimido[4,5-*c*]pyridazine (8):

A suspension of 4-cyano-3-hydroxyiminomethyleneamino-5-phenylpyridazine (**7**; 239 mg, 1 mmol) in water (5 ml) is heated under reflux for 2 h. The precipitate formed is collected, after cooling, by suction and washed with water; yield: 210 mg (88%); m.p. 222–226°C (ethanol).

$C_{12}H_9N_5O$	calc.	C 60.24	H 3.79	N 29.29
(239.2)	found	59.98	4.01	29.35

^{1}H-NMR (DMSO-d_6/TMS 105°C): δ = 7.32 (br s, 5 H$_{arom}$); 7.70 (s, 1 H, 3-H); 8.71 ppm (s, 1 H, 7-H).

MS (70 eV): *m/e* = 239 (M$^+$).

7*H*-2,3,4,6,7-Pentaazabenz[*d,e*]anthracene (9):

Method A: A solution of 3-amino-5-phenyl-4-(tetrazolyl-5)pyridazine (**10**; 478 mg, 2 mmol) and diethoxymethyl acetate (1 ml) in toluene (1 ml) is heated under reflux for 5 h. The precipitate formed is collected, after cooling, by filtration and washed with methanol; yield: 265 mg (60%); m.p. > 300°C (methanol/dimethylformamide).

$C_{12}H_7N_5$ (221.2) calc. C 65.15 H 3.19 N 31.66 found 64.97 3.04 31.37

^{1}H-NMR (DMSO-d_6/TMS): δ = 7.3–7.8 (m, 3 H, 8-H, 9-H, 10-H); 8.35–8.50 (m, 1 H, 11-H); 8.33 (s, 1 H, 5-H); 9.83 ppm (s, 1 H, 1-H).

MS: *m/e* (70 eV) = 221 (M^+).

Method B: A solution of 3-amino-5-phenyl-4-(tetrazolyl-5)pyridazine (**10**; 239 mg, 1 mmol) and triethyl orthoformate (5 ml) is heated under reflux for 8 h. The precipitate formed is collected, after cooling, by suction, washed with ethanol and recrystallized from a mixture of methanol and dimethylformamide; yield: 71 mg (32%).

Method C: A solution of 4-phenyl-5-hydroxyaminopyrimido[4,5-*c*]pyridazine (**8**; 119 mg, 0.5 mmol) and acetic anhydride (4 ml) is heated under reflux for 2 h. The mixture is cooled, the product is collected by suction and recrystallized from a mixture of methanol and dimethylformamide; yield: 46 mg (42%).

3-Amino-5-phenyl-4-(tetrazolyl-5)-pyridazine (10):
To a suspension of 3-amino-5-phenylpyridazine-4-carboxamidrazone (**3**; 228 mg, 1 mmol) in a mixture of water (4 ml) and acetic acid (5 ml), a solution of sodium nitrite (150 mg) in water (2 ml) is added dropwise at 0°C. The mixture is left for 2 h at room temperature. The precipitate formed is collected by suction; yield: 177 mg (74%); m.p. 278–280°C (ethanol/water).

$C_{11}H_9N_7$ (239.2) calc. C 55.22 H 3.79 N 40.99 found 55.41 3.80 41.08

^{1}H-NMR (DMSO-d_6/TMS): δ = 5.6–6.25 (br s, 3 H, NH, NH_2); 7.15–7.7 (m, 5 H_{arom}); 8.77 ppm (s, 1 H, 6-H).

MS (70 eV): *m/e* = 239 (M^+).

3-Hydroxyiminomethyleneamino-5-phenylpyridazine-4-carboxamide Oxime (13):
To a suspension of 4-cyano-3-(*N,N*-dimethylaminomethyleneamino)-5-phenylpyridazine (**2**; 126 mg, 0.5 mmol) in anhydrous ethanol hydroxylamine hydrochloride (100 mg) is added and the mixture is left at room temperature for 16 h. The volatile components are evaporated *in vacuo* to give **13**; yield: 88 mg (69%); m.p. 220–224°C (water).

$C_{12}H_{12}N_6O_2$ (272.3) calc. C 52.93 H 4.44 N 30.87 found 52.68 4.68 30.64

^{1}H-NMR (DMSO-d_6/TMS): δ = 6.0 (br s, 2 H, NH_2); 7.20–7.70 (m, 5 H_{arom}); 8.06 (d, 1 H, J = 10.2 Hz, CHNH); 8.84 (d, 1 H, J = 10.2 Hz, CHNH); 8.85 (s, 1 H, 6-H); 9.83 (s, 1 H, NOH); 10.48 (s, 1 H, NOH).

MS (70 eV): *m/e* = 272 (M^+).

3-Acetoxyiminomethylamino-5-phenylpyridazine-4-carboxamide *O*-acetyl Oxime (14):
A mixture of 3-hydroxyiminomethyleneaminopyridazine-4-carboxamide oxime (**13**; 256 mg, 1 mmol) and acetic anhydride (3 ml) is stirred at room temperature for 1 h. Ether (5 ml) is added to the mixture and the precipitate collected by suction to give **14**; yield: 206 mg (58%); m.p. 145–147°C (ethanol/carbon tetrachloride).

$C_{16}H_{16}N_6O_4$ (356.3) calc. C 53.93 H 4.53 N 23.58 found 53.95 4.49 23.39

^{1}H-NMR (DMSO-d_6/TMS): δ = 2.13 (s, 3 H, $COCH_3$); 2.17 (s, 3 H, $COCH_3$); 7.16 (br s, NH); 7.35–7.85 (m, 5 H_{arom}); 8.66 (d, 1 H, J = CHNH); 9.20 (s, 1 H, 6-H); 9.45 ppm (d, 1 H, J = 10.5 Hz, CHNH).

4-Amino-1,2,4-triazolo[1′,5′:2,3]pyridazino[4,5-*c*]quinoline (15):
A solution of 3-acetoxyiminomethylamino-5-phenylpyridazine-4-carboxamide O-acetyl oxime (**14**; 356 mg, 1 mmol) in acetic acid (5 ml) is heated unter reflux for 3 h. The volatile components are evaporated *in vacuo* and the precipitate, which is formed after addition of ethanol (4 ml) to the oily residue, is collected by suction to afford **15**; yield: 132 mg (56%); m.p. 327–330°C (ethanol/chloroform).

$C_{12}H_8N_6$ (236.2) calc. C 61.01 H 3.41 N 35.57 found 61.09 3.29 35.30

^{1}H-NMR (CF_3COOH/TMS): δ = 8.55 (m, 4 H, 9-H, 10-H, 11-H, 12-H); 9.55 (s, 1 H, 1-H); 10.50 ppm (s, 1 H, 5-H);

MS (70 eV): *m/e* = 236 (M^+).

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[1] Stanovnik, B., Štimac, A., Tišler, M., Verček, B. *J. Heterocyclic Chem.* **1982**, *19*, 577.
[2] Stanovnik, B., Bajt, O., Belčič, B., Koren, B., Prhavc, M., Štimac, A., Tišler, M. *Heterocycles* **1984**, *22*, 1545.
[3] Kočevar, M., Stanovnik, B., Tišler, M. *J. Heterocyclic Chem.* **1981**, *15*, 293.
[4] Kočevar, M., Stanovnik, B., Tišler, M. *Tetrahedron* **1983**, *39*, 823.
[5] For reviews on recently developed syntheses in this area see: Stanovnik, B. *Chemicke Zvesti (Chemical Papers)* **1982**, *36*, 693; *C.A.* **1983**, *98*, 71962.
Tišler, M. *Heterocycles* **1983**, *20*, 1951.
[6] Jurič, P., Kočevar, M., Stanovnik, B., Tišler, M., Verček, B. *Chemica Scripta* **1984**, *23*, 209; and references cited therein.
[7] Podergajs, S., Stanovnik, B., Tišler, M. *Synthesis* **1984**, 263; and references cited therein.
[8] Gewald, K., Oelsner, J. *J. prakt. Chem.* **1979**, *321*, 71.
[9] For a review see: Tišler, M., Stanovnik, B., in: *Condensed Pyridazines Including Cinnolines and Phthalazines*, Castle, R. N., Ed., John Wiley and Sons, New York 1973, pp. 761–1056.
[10] Styles, V. L., Morrision, R. W., Jr. *J. Org. Chem.* **1985**, *50*, 346; and references cited therein.