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STUDIES OF PYRIDAZINE COMPOUNDS, XXV.[1] REINVESTIGATION OF ACYLATION OF PYRIDAZINYLHYDRAZONES

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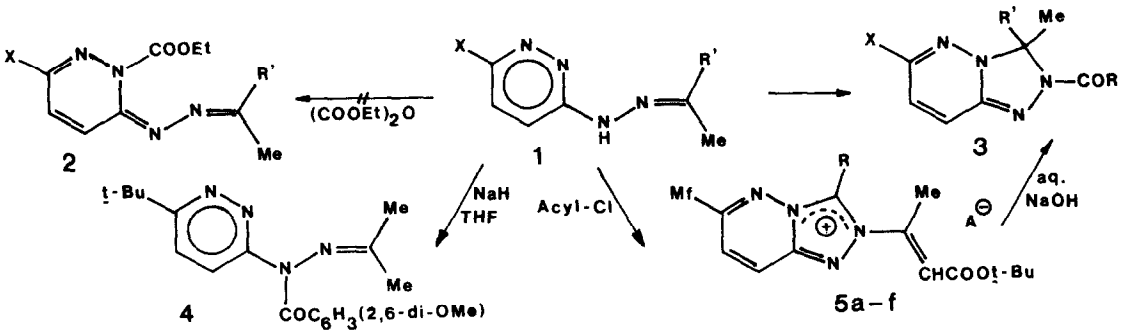
Abstract – *The acylation of morpholino substituted pyridazinylhydrazones afforded triazolo[4,3-b]pyridazinium salts. Structure elucidation by ir, ^{1}H- and ^{13}C-nmr spectroscopy, reaction mechanism and ring – chain tautomerism are discussed.*

Hydrazones react generally with acylating agents if there is an unsubstituted position on a nitrogen, and a variety of acylated hydrazones have been prepared under Schotten-Baumann conditions.[2,3] Aromatic aldehyde hydrazones can be trifluoroacetylated at azomethine carbon atom, too.[4] In our previous papers we reported on acylation of pyridazinylhydrazones.[5,6] Diethyl pyrocarbonate was chosen as the acylating agent which had provided scarlet compounds with 3-type structures assigned originally as 2-type endo-acylated products.



X: Cl, Mf, tBu, R': Me, CH_2COOEt, $CH_2COOtBu$ for compounds 1 – 3
X: Mf, R: 4-Cl-Ph (a), 4-OMe-Ph (b), 3-CF_3-Ph (c), 4-NO_2-Ph (d), 2-Cl-Ph (e) and $ClCH_2$ (f) for compounds 3a-c,e and 5a-f (Mf: morpholino)

Scheme 1

*Author to whom correspondence should be addressed (synthesis: P. M., spectroscopy: P. S.).

Abdulla et al described the reinvestigated structure of these compounds as triazolo[4,3-b]pyridazines 3 on the basis of X-ray analysis.[7] Furthermore, they reported on the formation of the benzoyl derivative 4 (Scheme 1).

On the basis of our earlier experiments on cyclization of pyridazinylhydrazones[8] it was clear that the substituent at the position 6 of the pyridazine ring has a strong influence on the acylation, too. Now, we decided to investigate the acylation of pyridazinylhydrazone 1a (X; Mf, R'; $CH_2COOtBu$) where the morpholino (Mf) moiety can play an important role in the acylation due to its strong conjugative electron-releasing character.

Reaction of β-keto ester hydrazones with acyl chlorides

Acylation of 1a with acyl chlorides in anhydrous benzene at elevated temperatures (that is under Abdulla's conditions) avoided the formation of 3-type compounds – as we expected. The facile reaction, however resulted in the cyclized triazolo[4,3-b]pyridazinium salts 5a-f as the only products in moderate to high yield (Scheme 1). Compound 1a, however, failed to react with 2,6-dichlorobenzoyl chloride neither to 3 nor to 5 due to steric hindrance. The anion exchange of 5a by aqueous perchloric acid resulted in a 5a-type salt containing ClO_4^- moiety as anion.

The structure of type 5 follows from the spectral data (c.f. Tables 1 and 2) straightforward;

a) Instead of the AB-spectrum (2xd with the interval 2.69-2.82 ppm) of methylene hydrogens (in R') in 3a-c,e the downfield shifted signal of an olefinic hydrogen appears in the ^{1}H-nmr spectrum of 5a-f between 6.15 and 6.8 ppm with 1H-intensity. Of course, the analogous change (from ∿40.5 ppm to ∿121.5 ppm) in the ^{13}C-nmr spectra can also be observed;

b) The neighbourhood of an unsaturated carbon causes a significant downfield shift of the β-methyl signal as compared to 3-type compounds, where this methyl group is attached to a saturated carbon (δCH_3 ∿2.65 and ∿2.00 ppm for the series 5 and 3, respectively). The corresponding downfield shift of the carbon line of the methyl group attached to C-β is about 6.0 ppm;

c) The delocalization of the electron deficiency involving the whole condensed skeleton and also the Mf nitrogen results in strong downfield shifts of both the NCH_2 and H-4,5 signals: NCH_2 ∿3.15 (3) and ∿3.75 (5), H-4 ∿6.75 (3) and ∿8.35 (5) and H-5 ∿6.6 (3) and ∿8.2 ppm (5), resp.;

d) The C-3 line of compounds 5a-f appears at about 156 ppm, instead of ∿150 ppm, measured for 3-type analogues, in accordance with the reduced electrondensity of the positively charged condensed skeleton in series 5;

e) The ester carbonyl line of compounds 5 (∿168 ppm) is upfield shifted as compared to the amide carbon signal of 3-type derivatives (∿163 ppm);

f) A very high shift difference of about 22 mmp (from 163.7 to 142 ppm) was

Table 1. Characteristic ir-bands (in KBr, cm^{-1}) and ^1H-nmr data (in $CDCl_3$ solution,[a] chemical shifts, $\delta_{TMS} = 0$ ppm, coupling constants, Hz) of compounds **1a**, **3a-c,e,g,h**, **5a-f**, **6a,b**, **7a,c** and **8** at 250 MHz

Compound	C=O band[b]	CH_3 (tBu) s(9H)	CH_3 Cβ s(3H)	NCH_2 t(2H)[c]	OCH_2 t(2H)[c]	H-4 d(1H)[d]	H-5 d(1H)[d]	CαH/CH_2 s/m(1/2H)[e]	Aromatic hydrogens (R) H-2',6'	H-3',5'	H-4'	OCH_3 s(3H)
1a[f]	1718	1.47	2.00	3.45	3.85	7.46	6.98	3.22	-	-	-	-
3a	1718	1.24	1.89	3.18	3.68	7.12	7.04	2.96 3.54	7.81[g]	7.48[g]	-	-
3b	1719	1.32	2.00	3.20	3.78	6.77	6.59	3.00 3.75	7.96[g]	6.88[g]	-	3.83
3c	1725	1.33	2.02	3.20	3.78	6.77	6.64	3.03 3.81	8.21[h]	7.50[i]	7.65[j]	
3e	1715	1.37	2.03	3.10	3.77	6.72	6.58	3.06 3.82		7.25-7.45[k]		
3g	-	-	1.80[l]	3.16	3.78	6.71	6.50	-	-	-	-	2.95[m]
3h	-	-	1.99[l]	3.19	3.79	6.74	6.61	-	7.85[g]	7.35[g]	-	-
5a	1718	1.47	2.58[n]	3.70	3.74	8,59	8.14	6.22[n]	7.99[g]	7.81[g]	-	-
5b	1716	1.50	2.53[n]	~3,8		8.52	8.22	6.40[n]	7.90[g]	7.15[g]	-	3.94
5c	1718	1.46	2.62[n]	3.75	3.80	8.35	8.27	6.44[n]	8.21[h]	7.82[i]	7.94[j]	-
5d	1720	1.42	2.56[n]	3.67	3.70	8.58	8.08	6.16[n]	8.19[g]	8.56[g]	-	-
5e	1718	1.45	2.59[n]	3.70	3.79	8.32[o]		6.30[n]	8.47[p]	~7.65[k]		-
5f	1707	1.56	2.78[n]	3.80	3.83	8.15	7.97	6.80[n]	-	-	-	5.35[r]
6a[f]	1705	1.39	2.39[n]	3.36	3.71	7.25	6.92	5.69[n]	7.57[g]	7.45[g]		3.82
6b[f]	1697	1.41	2.40[n]	3.45	3.82	6.9[o]		5.65[n]	7.65[g]	6.85[g]		
7a	-	-	-	3.57	3.77	7.42	8.17	-	8.41[g]	7.63[g]	-	-
7c	-	-	-	3.60	3.80	7.48	8.22	-	8.83[h]	~7.85[k]		-
8	1740	-	2.35	3.59	3.82	7.02	7.79	6.23	8.14[g]	7.47[g]	-	-

[a] Solvent: DMSO-d6 for **3a**, **5a,d**, **6a** and **7a,c**; [b] Further ir-bands: NH: ~3170 (**1a**), 3184 (**6a**), 3198 (**6b**); amide-I: 1616 (**3a**), 1610 (**3b,c**), 1651 (**3e**), 1620 (**3g**), 1600 (**3h**), 1675 (**6a,b**); C-O(Mf): 1115-1125 vs; tBu (**1a**, **3a-c,e**, **5a-f**, **6a,b**): 1135-1160 s-m; CF_3 (**3c**, **5a**, **7c**): 1335 s; NO_2 (**5d**):1529 s, 1352 s, 856 m; [c] Mf, $^3J(NCH_2,OCH_2) \approx 6$ Hz; [d] Pyridazine, ^3J(H-4,H-5): 9.5 Hz (**1a**, **6a**, **8**), 10.2 ± 0.1 (**3a-c,e,g,h**, **7a,c**), 10.5 ± 0,1 (**5a-f**); [e] Two d's (2x1H) for **3a,b,c,e** (AB-type spin-system), $^3J(A,B)$ = 15.1 ± 0.2 Hz; s(1H) for all other compounds (pyrazole-H for **8**); [f] NH, s(1H): 8.2 (**1a**), 9.3 (**6a**), 7.45 (**6b**); [g] A or B part of an AA'BB' m, $^3J(A,B)$: 8.6 ± 0,3 Hz; [h] H-2' ~s(1H) the H-6'signal is a ≈d(1H) at: 8.11(**3c**), 8.40(**5c**), 8.68(**7c**); [i] H-5', ~t(1H); [j] ~d(1H); [k] m of 4/3/2H-intensity (**3e**, **5e**, **7c**); [l] Intensity: 6H; [m] $N(CH_3)_2$, s(6H); [n] Split to d(CH_3) and qa(CαH) due to allylic coupling, $^4J(CH_3,CH\alpha) < 1$ Hz; [o] s(2H), the AB-spectrum appears in DMSO-d6 only; [p] H-6', m(1H); [r] CH_2, s(2H).

Table 2. ^{13}C-nmr chemical shifts (δ_{TMS} = 0 ppm) of compounds **1a**, **3a-c,e,g,h** , **5a-f**, **6a,b**, **7a,c** and **8** in $CDCl_3$ solution of 62.89 MHz.[a]

Compound	Morpholine ring		Pyridazine ring				tBu(R' group)		N-C(CH_3)-C_q group			ester	amide
	NCH_2	OCH_2	C-6	C-4,5		C-3	CH_3	C_q	$C_\beta CH_3$	$CH_\alpha(sp^2)$[b]	$C_q\beta$[c]	C=O	C=O[d]
1a	46.5	66.2	154.9	116.8[e]	116.8[e]	156.8	27.7	80.6	15.0	116.8[e]	142.7	168.9	
3a	46.5	65.6	143.9	122.9[e]	122.9[e]	149.9	27.6	79.9	23.8	41.8	83.3	167.5	162.8
3b	47.2	66.3	143.9	121.7	123.4	149.7	28.0	80.4	24.1	40.6	84.0	168.2	164.6
3c	47.2	66.3	144.3	122.0	123.2	149.9	27.9	80.8	24.0	40.3	84.0	168.1	163.6
3e	47.2	66.3	144.7	121.7	123.4	149.7	28.1	80.6	23.7	40.6	83.2	167.9	163.7
3g	47.0	66.1	142.0	120.5	123.2	149.9	-	-	-	23.0	85.4	-	157.8
3h	46.9	66.0	≈144[f]	121.6	122.9	149.7	-	-	-	23.1[f]	84.3[f]	-	163.6
5a[g]	45.4	65.6	145.9	123.7	124.3	156.3	27.7	82.2	17.4	121.6	141.3[h]	163.0	142.5[h]
5b	46.0	66.3	146.4	123.7	124.7	156.8	28.1	82.6	18.0	122.9	141.7[h]	163.3[i]	143.0[h]
5c	45.6	65.8	145.1	123.6	125.0	156.4	27.7	82.3	17.7	120.7	141.3[h]	162.7	141.5[h]
5d	45.2	65.4	145.5	123.5	124.3	156.1	27.5	82.1	17.4	121.5	141.1[h]	162.6	141.3[h]
5e	45.2	65.6	145.4	122.5	123.3	156.1	27.5	81.9	16.6	119.1	141.3[h]	162.6	140.4[h]
5f[g]	46.2	66.3	145.9	123.4[h]	123.9[h]	156.4	28.2	83.0	17.9	122.8[h]	141.2[i]	163.1	143.3[i]
6a[g]	47.7	67.6	154.4	117.8	119.1	159.0	29.6	81.4	18.9	112.8	156.2	167.1	171.5
6b	46.4	66.6	154.8	116.4	117.0	158.4	28.2	80.2	18.3	113.4	154.5	166.0	170.7
7a	45.6	65.6	145.1	114.2[j]	124.6	155.5	-	-	-	-	-	-	143.4
7c	46.5	66.3	146.1	113.0[j]	125.3	155.5	-	-	-	-	-	-	143.8
8	46.6	67.3	146.0	117.5[j]	123.5	160.7	-	-	15.8	99.8[k]	150.7[k]	163.6	150.2[k]

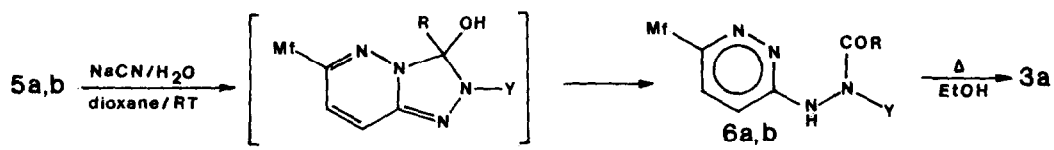
[a] Measuring frequency: 20.14 MHz for **1a**, **3a**, **5b,c,f**, **6a**, **7c** and **8**; Solvent: DMSO-d6 for **3a**, **5a,d**, **6a**, **7a** and **8**. Further signals: OCH_3: 55.3(**3b**), 55.9(**5b**), 55.4(**6b**); CF_3, qa, J(F,C) in Hz: 122.5 (255) for **5c**, 124.2 (273) for **7c**; NCH_3: 38.4(**3g**); CH_2Cl: 30.9(**5f**). Aromatic carbon signals for **3a-c,e,h**, **5a-e**, **6a,b**, **7a,c** and **8**: C-1': 134.2, 127.7, 136.0, 131.0, 133.9, 118.6, 111.0, 122.5, 130.5, 122.2, 136.2, 125.6, 127.9, 128.3; C-2' and C-6': 131.0, 131.7, 126.6 qa(3.6) and 132.9, 136.6 and 129.4, 130.9, 132.8, 132.6, 129.1 qa(3.8) and 134.6, 132.7, 133.4 and 134.1, 131.0, 130.8, 128.3[h],124.0 qa(4.0) and 129.2, 133.6; C-3' and C-5': 127.5, 112.9, 130.0 qa(32.5) and 128.1, 128.7 and 126.5, 127.5, 129.6, 115.2, 131.2 qa(33.5) and 129.8, 123.9, 129.5 and 127.8, 129.7, 113.7, 128.8[h], 132.4 qa(32.0) and 130.4, 130.9, C-4': 134.9, 161.3, 126.9 qa(3.8), 129.9, 136.0, 138.3, 163.6[i], 127.4 qa(3.8), 149.7, 134.2, 137.1, 162.4, 134.1, 126.1 qa(3.7), 141.2; [b] CH_2 in case of structure **3**; [c] $C_q(sp^3)$ for structure **3**, $C(sp^2)$ for all other compounds; [d] R-substituted carbon in the triazole ring for structure **5** and **7**; [e] Overlapping lines; [f] Broadened signal due to hindered rotation of the amide group; [g] Assignments were proved by DEPT measurements; [h,i] Reversed assignments may also be possible; [j] C-4; [k] Pyrazole ring.

observed for the R-substituted triazole carbon substituting the amide carbonyl carbon of 3-type compounds in series 5.

The remarkable difference in acylation between compounds containing electron-releasing groups (tBu by Abdulla and Mf by us) can be attributed to the +M effect of the Mf group increasing the electron density in the heteroaromatic ring. As a consequence, besides N^1-(exo)-acylation leading eg. to compound 4[7] the electrophile can also attack the endo (N-1 atom in pyridazine ring) or N^2-(exo)-nitrogen, too, resulting in acylated intermediates which can facilitate cyclization to 5-type compounds.

In order to form pseudobase from 5a,b reactions were carried out with sodium cyanide in water-dioxane mixture[9] at room temperature. These reactions resulted in the N-acylated products 6a,b by ring opening of the tetrahedral intermediate formed through nucleophilic attack of the solvent (Scheme 2).

This reaction can be regarded as a ring-chain tautomerism[10,11] proceeding via ring-opening of the pseudobase intermediate (Scheme 2). Ring opening may result in two different structures of type 2 or 6. The exclusive formation of 6a,b can be explained by stereoelectronic control, and/or by the difference in energy between an aromatic and a non-aromatic product.



Y: -C(Me)=CHCOOtBu, R: 4-Cl-Ph (a), 4-OMe-Ph (b)

Scheme 2

Spectral data proving structures 6a,b are as follows:

a) νNH and amide-I bands were found in the ir-spectra, and the broad NH signals in the ^{1}H-nmr spectra can also be identified;

b) The C-3,4,5,6 chemical shifts of 6a,b are practically the same as for 1a. Acylation of the pyridazine-N (2-type structure) or N-1 would cause significant differences in these shifts;

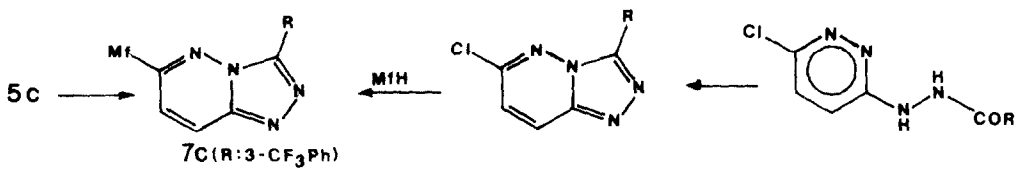
c) Characteristic shifts were observed for the ^{1}H- and ^{13}C-nmr signals of the methyl group attached to C-β, as well as for the C-β line. This latter shift is very large: instead of 142.7 ppm (1a) the C-β line appears at 156.2 and 154.5 ppm in the ^{13}C-nmr spectra of 6a and 6b, respectively. Consequently, the 4-substituted benzoyl group must be neighbouring to the Y-moiety (=CMe- group).

Heating of 6a in ethanol or ring-transformation of 5-type compounds by aqueous NaOH solution afforded 3-type compounds (Scheme 1, 2).*

* 3d can be, however, isolated only in an 1:1 mixture with 6d

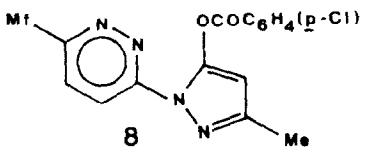
Conversion of 5a-d,f into 3a-d,f proceeds probably via ring-opening of compounds 5 to 6 followed by cyclization (see Experimental for 3a, Method B).

Treatment of 5c with NaCN in a water-dioxane mixture yielded 7c. This structure was proved by independent synthesis using partly a known method[12] (Scheme 3):



Scheme 3

Structure 7c was deduced from the lack of all spectral characteristics (ir, nmr) arising from the –CMe=COOtBu chain and from the very similar shifts of H-5 and C-3,5,6 as compared to the series 5.

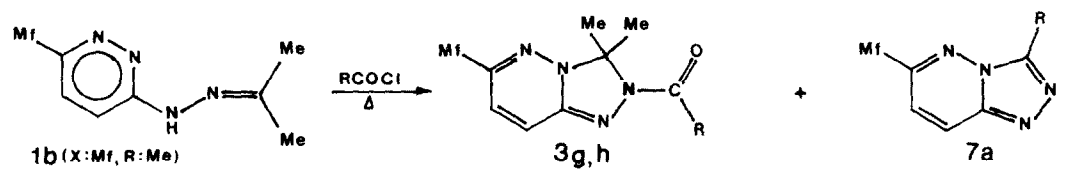


In contrast with the facile acylation in THF with NaH found by Abdulla,[7] the analogous Mf hydrazones did not appear to undergo N-acylation. Treatment of 1a with 4-chlorobenzoyl chloride in the presence of NaH (or $NaNH_2$) in THF or diethylether afforded the O-acylated pyrazole derivative 8.

Structure 8 was proved by the presence of ester bands in the ir-spectrum, and by the high frequency (1740 cm^{-1}) of the νC=O bands, further by the disappearance of the nmr-signals of the tBu-group and by the ^1H- and ^{13}C-nmr signals of the C-methyl-substituted pyrazole at 15.8 (CH_3) and 6.23 ppm (=CH) and at 99.8 (C-4), 150.2 and 150.7 ppm (C-3,5), respectively.

Reaction of alkylhydrazones with acyl chlorides

To compare the reactivity of the alkylhydrazones with that of the β-keto ester hydrazones, reaction was carried out with 1b. (X: Mf, R': Me). A remarkable difference in the way of acylation was found. Treatment with 4-chlorobenzoyl chloride or N,N-dimethylcarbamoyl chloride in benzene at elevated temperature afforded the 3-type compounds 3g,h (as major products) and the dealkylated 7a (Scheme 4).



a,h(R: 4-Cl-Ph); g(R: NMe_2)

Scheme 4

Compounds 3g,h show completely analogous ^{1}H- and ^{13}C-nmr spectra with 3a-c,e, while 7a has very similar nmr data to 7c.

Our findings suggest that not only the 6-substituent in the pyridazine ring but also the hydrazone moiety has a strong influence on the nature of the acylation of pyridazinylhydrazones.

EXPERIMENTAL

Ir spectra (in KBr discs): Bruker IFS-113v vacuum optic FT-spectrometer equipped with an Aspect 2000 computer. — ^{1}H- and ^{13}C-nmr spectra (in $CDCl_3$ or DMSO-d_6 solution at RT, using TMS as internal reference): Bruker WM-250 or Bruker WP 80 SY FT-spectrometer controlled by Aspect 2000 computer. — MS: Varian MAT SM 1.

Melting points are not corrected. All yields are preparative ones.

6-Morpholino-(3-substituted phenyl)-2-[1-(tertiary butoxycarbonyl)-1-propen-2-yl]-1,2,4-triazolo[3,4-b]pyridazinium salts (5a-f):

General procedure: A stirred mixture of 3 mmol hydrazone 1a[13] and 3 mmol acylchloride in 25 ml benzene was refluxed under N_2 for 2 h. After cooling, the solid was collected by filtration, washed with benzene, and dried to give 5a-f. Work up of the mother liquors by preparative TLC gave 6 % of 3b only in case of 5b.

N^2-(6-Morpholino-3-pyridazinyl)-N^1-[1-(tertiary butoxycarbonyl)-1-propen-2-yl]-(4-chloro- and -(4-methoxy-benzoic hydrazide) (6a,b):

A mixture of 2 mmol 5a,b and 2.4 mmol sodium cyanide in 12 ml of a 2:1 mixture of dioxane and water was stirred at RT for 24 h. After filtration, the solid was washed with water and recrystallized from ethanol yielding 6a,b.

2-(4-Chlorobenzoyl)-3-methyl-6-morpholino-3-(tertiary butoxycarbonylmethyl)-2,3-dihydro-1,2,4-triazolo[4,3-b]pyridazine (3a):

Method A: By thermal reaction of 6a: A stirred mixture of 200 mg 6a in 2 ml ethanol was heated at reflux for 10 h. After cooling, ethanol was evaporated in vacuo and the residue was chromatographed on 10 g silica using benzene and methanol as eluating solvents to give 50 mg (10 %) of a scarlet crystalline solid, m.p. 162-164 °C (acetonitrile-diethylether).

Method B: By ring closure of 6a under basic conditions: A mixture of 1 mmol 6a, 1.2 mmol NaOH in 2 ml water and 4 ml dioxane was stirred at RT for 7 h. After work-up with water and extraction with CH_2Cl_2 the reaction mixture was dried over $MgSO_4$. 3a was separated by preparative TLC on Kieselgel 60 HF_{254} plate using a 85:15 mixture of benzene and methanol as eluating solvent. Red cubes, m.p. 163-165 °C, in 21 % yield.

Method C: By ring-chain tautomerism of 5a: Reaction was carried out under the same conditions mentioned above (Method B). Red cubes, m.p. 162-4 °C, in 42 % yield. Synthesis of 3b,c,e was carried out by the same method, starting from 5b,c,e.

6-Morpholino-3-(3-trifluoromethylphenyl)-1,2,4-triazolo[4,3-b]pyridazine (7c):

Method A: by method C described for 6a, starting from 5c. White crystalls, m.p. 219-220 °C, in 16 % preparative yield.

Method B: Starting from N'-(6-chloro-3-pyridazinyl)-(3-trifluoromethyl-benzoic hydrazide) M.p. 142-144 °C, prepared from the corresponding pyridazinylhydrazine with 3-trifluoromethylbenzoyl chloride) can be cyclized to 6-chloro-3-(trifluoromethylphenyl)-1,2,4-triazolo [4,3-b]pyridazine by Pollak's and Tisler's method.[12] 1.5 g this product in 4.5 ml morpholine in the presence of 0.5 ml HMPA was heated at reflux (∿140 °C) for 5 h. After evaporation of the excess of morpholine in vacuo the residue was stirred with water, filtered and recrystallized from ethanol, yield: 1.1 g (64 %), m.p. 219-220 °C.

5-(4-Chlorobenzoyloxy)-3-methyl-1-(6-morpholino-3-pyridazinyl)pyrazole (8):

A mixture of 0.1 g (6 mmol) NaNH in 20 ml diethyl ether, 5 mmol 1a and 0.875 g (5 mmol) 4-chlorobenzoyl chloride was stirred at 10-20 °C for 150 min. After work-up with diluted HCl

Table 3. Physical data for compounds **1a**, **3a-c,e,g,h**, **5a-f**, **6a,b**, **7a,c** and **8**

Compound	M.p. °C	General formula	M.W.	Yield %	Elemental analysis, % Calculated/ Found C	H	N
1a	144-147	$C_{16}H_{25}N_5O_3$	335.40	54	57.29/57.32	6.78/6.85	20.88/20.86
3a	162-164[a]	$C_{23}H_{28}ClN_5O_4$	473.95	b	58.28/58.37	5.96/6.04	14.78/14.85
3b	185-187	$C_{24}H_{31}N_5O_5$	469.53	29	61.39/61.26	6.66/6.52	14.92/14.72
3c	128-129	$C_{24}H_{28}F_3N_5O_4$	507.50	16	56.80/56.84	5.50/5.72	13.80/13.68
3e	102-104	$C_{23}H_{28}ClN_5O_4$	473.95	56	58.28/58.42	5.96/6.09	14.78/14.73
3g	175-178[c]	$C_{14}H_{22}N_6O_2$	306.37	40	54.88/54.92	7.23/7.36	27.44/27.28
3h	207-209[d]	$C_{18}H_{20}ClN_5O_2$	373.84	21.5	57.83/57.85	5.39/5.52	18.74/18.66
5a	229-230[e]	$C_{23}H_{27}Cl_2N_5O_3$	492.40	76	56.10/55.94	5.53/5.59	14.22/14.25
5b	238-240[f]	$C_{23}H_{27}Cl_2N_5O_7$	556.40	68	49.65/49.68	4.89/4.85	12.59/12.47
5b	155-157[c]	$C_{24}H_{30}ClN_5O_4$	487.97	62	59.07/59.26	6.20/6.16	14.35/14.45
5c	224-226[e]	$C_{24}H_{27}ClF_3N_5O_3$	525.95	62.5	54.80/54.65	5.18/5.11	13.32/13.21
5d	211-212[g]	$C_{23}H_{27}ClN_6O_5$	502.95	75	54.92/54.87	5.41/5.54	16.71/16.62
5e	180-181[c]	$C_{23}H_{27}Cl_2N_5O_3$	492.40	78	56.10/55.92	5.53/5.63	14.22/14.26
5f	216-218[e]	$C_{18}H_{25}Cl_2N_5O_3$	430.33	38.5	50.24/50.25	5.86/5.93	16.28/16.13
6a	158-160[h]	$C_{23}H_{28}ClN_5O_4$	473.95	47.5	58.28/58.18	5.95/6.07	14.78/14.87
6b	155-157[h]	$C_{24}H_{31}N_5O_5$	469.53	15	61.39/61.55	6.66/6.81	14.92/14.84
7a	245-246[i]	$C_{15}H_{14}ClN_5O$	315.76	3	57.05/56.94	4.47/4.40	22.18/22.23
7c	219-220[h]	$C_{16}H_{14}F_3N_5O$	349.31	64	55.01/55.14	4.04/3.89	20.05/19.97
8	186-187[h]	$C_{19}H_{18}ClN_5O_3$	399.83	27.5	57.07/57.18	4.54/4.46	17.52/17.40

[a] chromatographed over silica; [b] see Method A-C; [c] benzene; [d] 7:3 isopropanol-ether; [e] methanol; [f] **5a** perchlorate salt, white powder (water); [g] benzene-acetone; [h] ethanol; [i] acetonitrile.

the product was extracted with 3 x 25 ml CH_2Cl_2, dried to give 0.55 g (27.5 %) **8**, m.p. 186-187 °C (ethanol).

Triazolo[4,3-b]pyridazines **3g,h** *and* **7a** *from isopropylidenehydrazones*

Starting from **1b** (X: Mf, R': Me)[14] by method described for **5a-f** gave the title compounds.

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REFERENCES and NOTES

1. Part XXIV: Kasztreiner, E.; Szilágyi, G.; Magyar Kémikusok Lapja (in Hungarian), 1988, 43, 197.
2. Smith, P. A. S.; Clegg, J. M.; Lakritz, J.; J. Org. Chem., 1958, 23, 1595.
3. Gillis, B. T.; Schimmel, K. F.; J. Org. Chem., 1962, 27, 413.
4. Kamitor, Y.; Hojo, M.; Masuda, R.; Fujitani, T.; Ohara, S.; Yokohama, T.; J. Org. Chem., 1988, 53, 129.
5. Mátyus, P.; Szilágyi, G.; Kasztreiner, E.; Sohár, P.; Acta Chim. Acad. Sci. Hung., 1981, 106, 205.
6. Mátyus, P.; Szilágyi, G.; Kasztreiner, E.; Sóti, M.; Sohár, P.; Acta Chim. Acad. Sci. Hung., 1982, 109, 237.
7. Abdulla, R. F.; Jones, N. D.; Swartzenbruder, J. K.; Chem. Ber., 1985, 118, 5009.
8. Szilágyi, G.; Sohár, P.; Langó, J.; Zólyomi, G.; Tetrahedron, 1989, 45, 1973.
9. NaCN in water-dioxane mixture is a very useful chemical tool to obtain pseudobases, Korbonits, D.; private communication.
10. Beke, D.; in Adv. Heterocycl. Chem., 1963, 1, 167.
11. Bunting, J. W.; in Adv. Heterocycl. Chem., 1979, 25, 1.
12. Pollak, A.; Tisler, M.; Tetrahedron, 1966, 22, 2073.
13. Szilágyi, G.; Kasztreiner, E.; Mátyus, P.; Kosáry, J.; Czakó, K.; Cseh, Gy.; Huszti, Zs.; Tardos, L.; Kósa, E.; Jaszlits, L.; Eur. J. Med. Chem., 1984, 19, 111.
14. Bellasio, E.; Parravicini, F.; Testa, E.; Il Farmaco, Ed. Sci., 1969, 24, 919.