INVERSE-ELECTRON-DEMAND DIELS-ALDER REACTIONS OF CONDENSED PYRIDAZINES, 4.[1] SYNTHESIS AND CYCLOADDITION REACTIONS OF 1,4-BIS(TRIFLUOROMETHYL)PYRIDO[3,4-*d*]PYRIDAZINE

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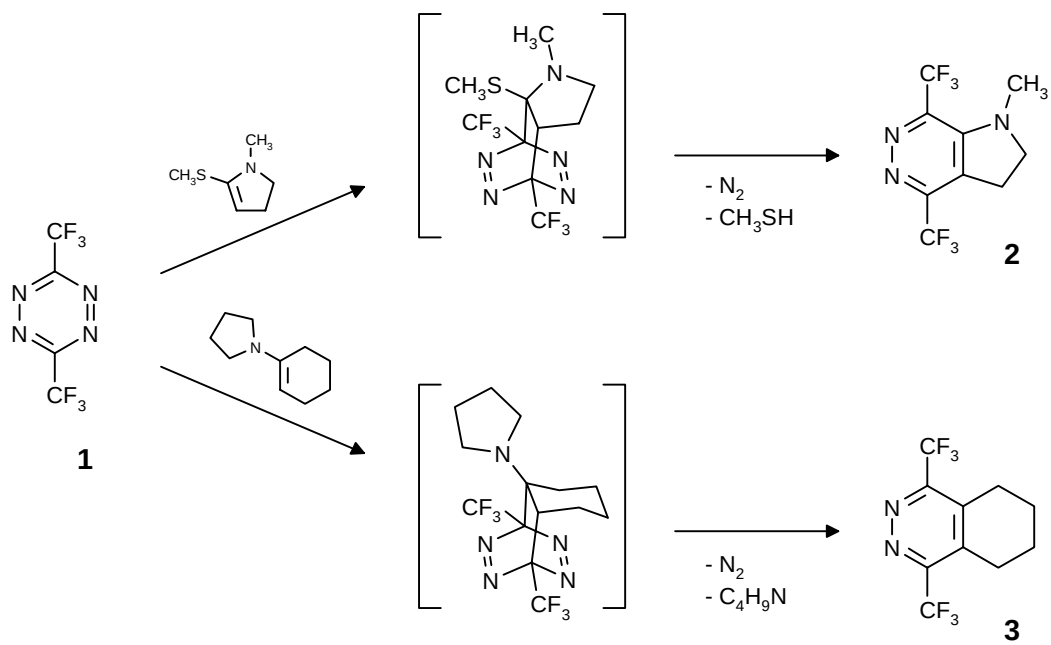
Abstract - The title compound (**8**) was prepared by a [4+2] cycloaddition reaction of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine (**1**) with a 4-piperidone-derived enamine and subsequent aromatization of the tetrahydro compound (**7**). The azadiene reactivity of **8** was investigated employing enamines and a ketene-*N*,*S*-acetal as electron-rich dienophiles. A series of new condensed isoquinolines (**10**, **11**, **12a,b**, **13**) was obtained and one of them (**13**) was characterized by X-ray structure determination.

The utilization of inverse-electron-demand ($LUMO_{diene}$-controlled) Diels-Alder reactions of π-electron-deficient *N*-heteroaromatics with electron-rich dienophiles has become a well-established synthetic tool and thus continues to attract considerable interest.[2] In the course of a program aimed at the investigation of condensed pyridazines with respect to their ability to undergo such [4+2] cycloaddition reactions,[1,3,4] we became interested in the synthesis of 1,4-bis(trifluoromethyl)pyrido[3,4-*d*]pyridazine. In this so far unknown triazanaphthalene derivative, the pyridazine ring should be activated as an azadiene component (towards electron-rich dienophiles) by the two strongly electron-withdrawing trifluoromethyl groups as well as by the annelation of a second π-electron-deficient heteroaromatic ring. The latter effect has been demonstrated recently with various pyridine- and pyridazine-fused 1,2-diazines.[1,3,4] Thus, the title compound should have a relatively low

LUMO energy and should be suitable for the construction of higher annelated ring systems (one of the major aims of our current studies) by [4+2] cycloaddition reactions with appropriate dienophiles.

For the preparation of the target azadiene, we again chose the [4+2] cycloaddition methodology, using readily available 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine[5] (**1**) as the starting material. This extremely reactive azadiene has been shown in numerous examples, in particular by Seitz and coworkers, to be a very useful precursor for a wide variety of pyridazine derivatives.[6-16] To further evaluate its synthetic utility, **1** was allowed to react at room temperature with a cyclic ketene *N*,*S*-acetal (1-methyl-2-methylthio-2-pyrroline) as well as with a cyclic enamine (1-pyrrolidino-1-cyclohexene) as electron-rich dienophiles. In each case, the starting material was completely consumed after a few minutes, and the expected annelated pyridazines (**2**) or (**3**), respectively, could be isolated in satisfactory yields (Scheme 1).

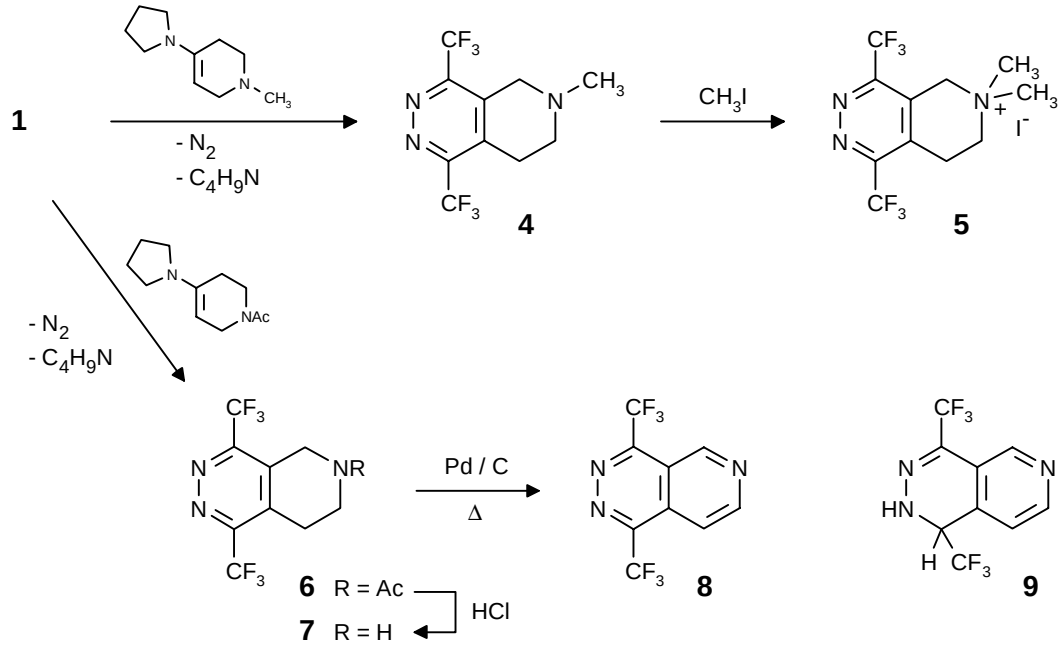
Scheme 1



For the construction of the pyrido[3,4-*d*]pyridazine skeleton, employment of a 4-piperidone-derived enamine as the dienophile component in an inverse-electron-demand Diels-Alder reaction with **1** was considered a promising approach. Thus, in a preliminary experiment, the tetrazine (**1**) reacted with a slight excess of 1,2,5,6-tetrahydro-1-methyl-4-pyrrolidinopyridine in dichloromethane at room temperature. Indeed, the product isolated in about 60% yield turned out to be the expected tetrahydropyrido[3,4-*d*]pyridazine derivative (**4**), obviously resulting from loss of N_2 from an intermediate cycloaddition adduct and subsequent spontaneous elimination of pyrrolidine. As compound (**4**) proved to be unstable and could not be recrystallized, the base

was treated with methyl iodide to give the quaternary salt (**5**) which was obtained as stable crystals and could be easily characterized.

Scheme 2



In order to gain access to the fully aromatic pyrido[3,4-*d*]pyridazine system, a 4-piperidone enamine with a conveniently removable nitrogen substituent was to be used. For this purpose, we chose 1-acetyl-1,2,5,6-tetrahydro-4-pyrrolidinopyridine as dienophile in the cycloaddition reaction with **1**. In an analogous manner as described for the preparation of **4**, the *N*-acetyl compound (**6**) was obtained in a yield of 74% after chromatographic work-up. Removal of the acetyl group was easily accomplished without affection of the trifluoromethyl substituents by refluxing **6** in aqueous hydrochloric acid. Initial attempts to aromatize the secondary amine (**7**) by the method described by Marcelis and van der Plas[17] for the preparation of a 1,6-naphthyridine derivative (using iodine as oxidant) gave unsatisfactory results. However, we found that refluxing **7** in xylene for 24 hours in the presence of 10% palladium on charcoal (conditions which have been employed recently for the synthesis of 6-azaquinazolines[18]) effectively converted the tetrahydro compound into the desired 1,4-bis(trifluoromethyl)pyrido[3,4-*d*]pyridazine (**8**) in 76% yield.

When this dehydrogenation reaction was carried out on a multigram scale, the time required for complete consumption of the starting material was significantly longer and, moreover, we were able to isolate an intermediate dihydropyrido[3,4-*d*]pyridazine derivative (**9**) by column chromatography. Interestingly, from the

^{1}H-nmr spectrum it became evident that in this compound the pyridine ring is fully aromatic whereas a dihydropyridazine subunit must be present. One of the two hydrogen atoms in the latter could be easily identified as an NH (by D_2O exchange), the other proton gives a quartet (δ = 4.94 ppm) with a $^3J_{H\text{-}F}$ coupling constant of 7.6 Hz and thus has to be assigned to a CH-CF_3 structure. By means of nuclear Overhauser enhancement (nOe) difference spectroscopy, we finally could establish the structure of **9** as the 1,2-dihydro-pyrido[3,4-*d*]pyridazine derivative displayed in Scheme 2: Saturation of the signal at 4.94 ppm led to a significant nOe for the doublet of H-8 at 7.26 ppm (Figure 1).

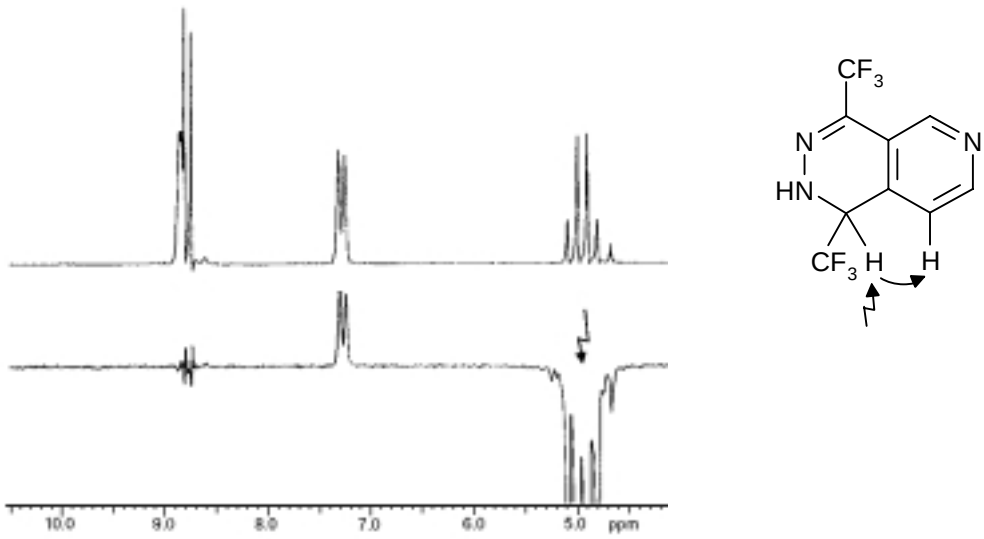
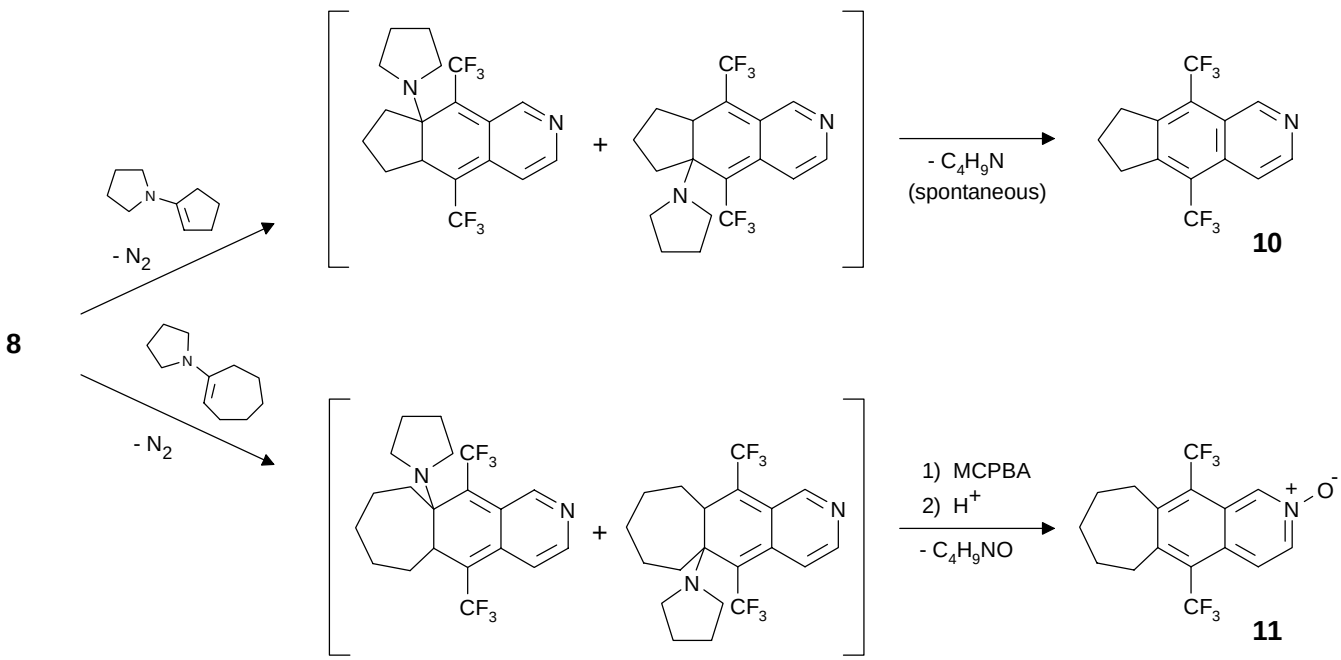


Figure 1. 80 MHz ^{1}H-nmr spectrum (upper trace) and nOe difference spectrum of **9** ($CDCl_3/D_2O$; 25°C)

With the azadiene (**8**) now readily available, its reactivity towards electron-rich dienophiles was investigated. Thus, **8** was treated with an excess of 1-pyrrolidino-1-cyclopentene in 1,4-dioxane. Whereas at room temperature no reaction was observed, refluxing of the mixture led to complete conversion within 1 hour. The product isolated in satisfactory yield has the structure of a cyclopentene-fused isoquinoline (compound **10**), according to ^{1}H-nmr and mass spectroscopy as well as elemental analysis. For a probable dihydroisoquinoline intermediate (still bearing the pyrrolidine moiety), two regioisomeric structures can be formulated, both leading to the final product (**10**) by a 1,2-elimination step (Scheme 3). In contrast to the successful transformation **8** → **10**, employment of the homologous cyclohexanone-derived enamine (which is known to exhibit significantly lower reactivity than the corresponding five-membered dienophile[3,4,19]) did not lead to any conversion even on prolonged refluxing. On the other hand, with 1-pyrrolidino-1-cycloheptene and the azadiene (**8**), the expected [4+2] cycloaddition reaction took place smoothly, leading to a reaction product in 72% yield after a reaction

time of 3 hours at reflux temperature. In contrast to the case of the five-membered analog (**10**), however, here the reaction stops at the stage of a dihydroisoquinoline derivative. According to the ^{1}H-nmr spectrum of the crude product, it is a mixture of both regioisomers in a ratio of 2 : 3. So far, no assignment of the two structures to the major and the minor component could be made by spectroscopy. Moreover, the mixture could not be separated chromatographically nor by recrystallization. Initial attemps to effect pyrrolidine elimination from the dihydroisoquinoline compounds in order to give a single aromatic product were unsuccessful: refluxing the material in toluene/trifluoroacetic acid as well as heating a neat sample to >200°C (methods which have been employed recently for similar conversions[3]) only resulted in slow decomposition. However, the aromatization step finally could be performed by *N*-oxidation of the pyrrolidine nitrogen atom with *m*-chloroperbenzoic acid[4,20] and subsequent refluxing of the mixture in 1-propanol/ trifluoroacetic acid (elimination of *N*-hydroxy-pyrrolidine). It should be noted that under these conditions not only the pyrrolidine nitrogen is oxidized but also the isoquinoline C=N- unit is converted into the corresponding *N*-oxide, thus leading to compound **11** (Scheme 3).

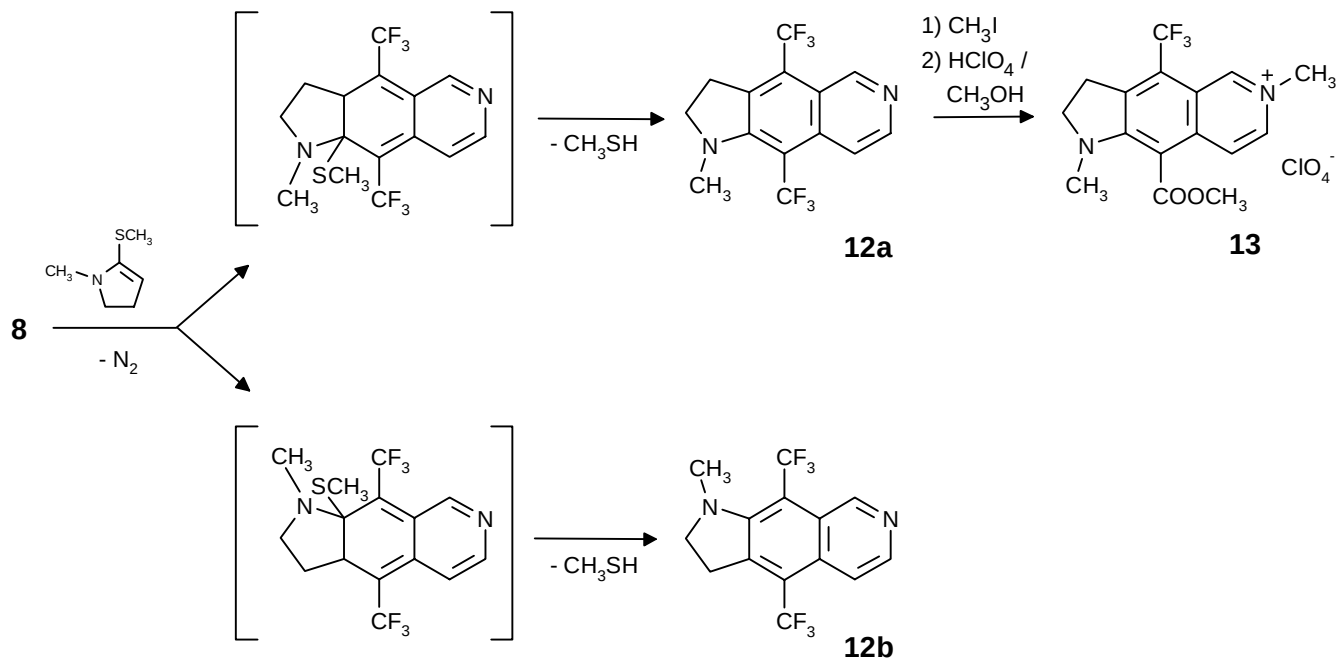
Scheme 3



As an extension to the investigations described above, the pyrido[3,4-*d*]pyridazine (**8**) was also reacted with 1-methyl-2-methylthio-2-pyrroline as a dienophile. In this case, formation of two isomeric pyrroline-annelated isoquinolines (after elimination of molecular nitrogen and methanethiol from the initially formed cycloadducts) had to be anticipated. Indeed, after a reaction time of only 30 minutes at room temperature, **8** was completely

consumed and two new compounds were formed, as indicated by tlc. The mixture thus obtained in an overall yield of 65% could be separated by medium pressure liquid chromatography to afford two compounds in a ratio of 1 : 2.3. Elemental analyses and mass spectra confirmed the expected molecular formula ($C_{14}H_{10}N_2F_6$) for both products. Although from the ^{1}H-nmr spectra it is obvious that the structures of the dihydropyrroloisoquinolines (**12a**) and (**12b**) have to be assigned to these new compounds, the observed chemical shifts as well as the splitting patterns of the corresponding proton signals - expectedly - are very similar and thus do not permit an unequivocal discrimination between **12a** and **12b.** As both isomers could be obtained only as microcrystalline powders, an attempt was made to convert the major component into a derivative suitable for X-ray crystal structure determination. Thus, the major isomer was treated with an excess of methyl iodide to give a quaternary salt. The ^{1}H-nmr spectrum of the crude product indicated that the newly introduced *N*-methyl group is located at the isoquinoline nitrogen atom. As also this compound could not be recrystallized in a satisfactory way, we attempted to exchange the iodide anion by perchlorate. For this purpose, the material was treated with perchloric acid in methanol, and the crystals thus obtained were recrystallized from the same solvent. Interestingly, under these conditions not only the anion was exchanged, but also one of the trifluoromethyl groups was selectively transformed into a methyl ester moiety, as indicated by ^{1}H-nmr, ir and mass spectroscopy. The structure of the perchlorate (**13**) finally could be firmly established by means of X-ray crystallography (see Figure 2), thus enabling us to assign the structures of the cycloaddition products (**12a**) (major component) and (**12b**) (minor component) as displayed in Scheme 4.

Scheme 4



The preferential formation of isomer (**12a**) in the cycloaddition reaction of **8** with 1-methyl-2-methylthio-2-pyrroline is in agreement with the values for the LUMO p_z coefficients as well as with those for the partial charges of the involved pyridazine carbon atoms (C-1 and C-4), with respect to the values for the HOMO p_z coefficients and electron densities of the dienophile,[21] which we calculated using the AM1 method[22] as implemented in the AMPAC computer program.[23] It should be noted, however, that such estimations regarding the regiochemistry of [4+2] cycloaddition reactions should be made very cautiously; for a more accurate exploration of mechanistic/regiochemical aspects of such transformations, higher-level *ab initio* calculations should be employed as proposed recently.[24] Although the observed azadiene reactivity of **8** towards electron-rich dienophiles is somewhat lower than that of the tetrazine (**1**), as reflected by the corresponding LUMO energies (compound **8**: -2.42 eV, compound **1**: -2.80 eV; calculated with AM1[22]), the pyrido[3,4-*d*]pyridazine (**8**) has been shown to be a suitable building block for the construction of fused isoquinolines *via* an inverse-electron-demand Diels-Alder pathway.

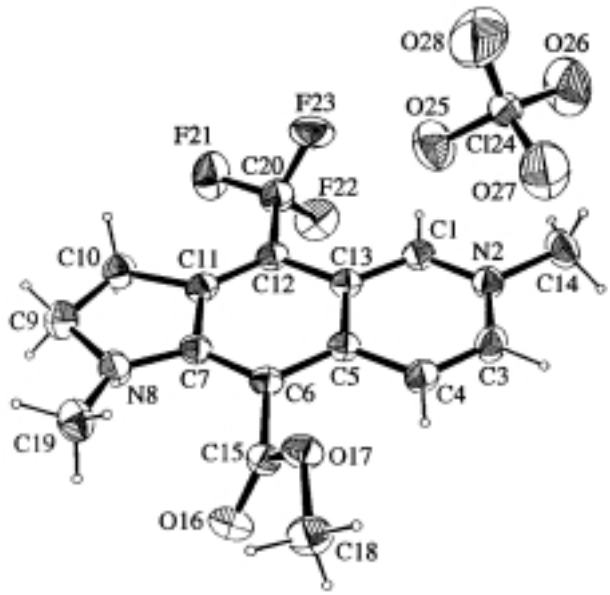


Figure 2. Crystal structure of **13** (30% ellipsoids, arbitrary atom numbering)

EXPERIMENTAL

All melting points were determined on a Kofler hot-stage microscope and are uncorrected. Ir spectra were recorded for KBr pellets on a Perkin-Elmer 1605 FT-IR instrument; ^{1}H-nmr spectra were recorded on a Varian Unity*plus* 300 (300 MHz) or a Bruker AC 80 (80 MHz) spectrometer (TMS as internal reference, δ values in ppm). Mass spectra were obtained with a Hewlett-Packard 5890A/5970B-GC/MSD spectrometer. Column

chromatography was done on Merck Kieselgel 60, 0.063-0.200 mm, medium pressure liquid chromatography (MPLC) was carried out on Merck LiChroprep Si 60, 0.040-0.063 mm (detection at 280 nm). Light petroleum refers to the fraction of bp 50-70°C. Microanalyses were performed at the Institute of Physical Chemistry (Microanalytical Laboratory), University of Vienna.

4,7-Bis(trifluoromethyl)-2,3-dihydro-1-methyl-1*H*-pyrrolo[2,3-*d*]pyridazine (**2**)

A solution of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine[5] (**1**) (218 mg, 1 mmol) and freshly prepared 1-methyl-2-methylthio-2-pyrroline[25] (258 mg, 2 mmol) in dry 1,4-dioxane (10 ml) was stirred at room temperature for 30 min under argon atmosphere. The volatile components were removed under reduced pressure and the residue was subjected to column chromatography (light petroleum/ethyl acetate, 7:3). Recrystallization from light petroleum/ethyl acetate afforded 139 mg (51%) of colorless needles, mp 112-113°C. *Anal.* Calcd for $C_9H_7N_3F_6$: C, 39.86; H, 2.60; N, 15.50. Found: C, 39.86; H, 2.39; N, 15.26. Ms: *m/z* (rel. int.) 272 (10%), 271 (M^+, 100), 270 (79), 252 (11), 136 (11). ^{1}H-Nmr (80 MHz, $CDCl_3$) δ: 4.10-3.70 (m, 2 H, N-CH_2-C), 3.50-3.10 (m, 2 H, Ar-CH_2-C), 3.14 (q, J_{H-F} = 2.3 Hz, 3 H, CH_3).

1,4-Bis(trifluoromethyl)-5,6,7,8-tetrahydrophthalazine (**3**)

To an ice-cooled solution of **1** (218 mg, 1 mmol) in dry dichloromethane (10 ml) was added dropwise a solution of 1-pyrrolidino-1-cyclohexene[26] (180 mg, 1.2 mmol) in dry dichloromethane (5 ml), then the mixture was stirred at room temperature for 20 min under argon atmosphere. The volatile components were removed under reduced pressure and the residue was subjected to column chromatography (light petroleum/ethyl acetate, 9:1). Recrystallization from light petroleum afforded 210 mg (78%) of colorless crystals, mp 59-62°C. *Anal.* Calcd for $C_{10}H_8N_2F_6$: C, 44.46; H, 2.98; N, 10.37. Found: C, 44.53; H, 2.85; N, 10.30. Ms: *m/z* (rel. int.) 271 (11%), 270 (M^+, 100), 214 (10). ^{1}H-Nmr (80 MHz, $CDCl_3$) δ: 3.30-2.70 (m, 4 H, Ar-CH_2-C), 2.10-1.70 (m, 4 H, C-CH_2-C).

1,4-Bis(trifluoromethyl)-5,6,7,8-tetrahydro-6-methylpyrido[3,4-*d*]pyridazine (**4**)

To an ice-cooled solution of **1** (218 mg, 1 mmol) in dry dichloromethane (10 ml) was added dropwise a solution of 1,2,5,6-tetrahydro-1-methyl-4-pyrrolidinopyridine[27] (200 mg, 1.2 mmol) in dry dichloromethane (5 ml), then the mixture was stirred at room temperature for 20 min under argon atmosphere. The volatile components were removed under reduced pressure and the residue was subjected to column chromatography (light petroleum/ethyl acetate, 1:1) to give 168 mg (59%) of a pale yellow solid, mp 72-74°C, which slowly

turned dark. Ms: *m/z* (rel. int.) 285 (M^+, 51%), 284 (100), 282 (16). ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 3.73-3.65 (m, 2 H, Ar-CH_2-N), 3.12-3.02 (m, 2 H, Ar-CH_2-C), 2.70 (t, *J* = 5.9 Hz, 2 H, C-CH_2-N), 2.45 (s, 3 H, CH_3).

1,4-Bis(trifluoromethyl)-5,6,7,8-tetrahydro-6,6-dimethylpyrido[3,4-*d*]pyridazin-6-ium Iodide (**5**)

A solution of **4** (142 mg, 0.5 mmol) and methyl iodide (2.84 g, 20 mmol) in tetrahydrofuran (6 ml) was stirred at room temperature for 12 h. The solvent was evaporated and the residue was recrystallized from methanol to give 128 mg (60%) of colorless needles, mp 255-270°C (dec.). *Anal.* Calcd for $C_{11}H_{12}N_3F_6I$: C, 30.93; H, 2.83; N, 9.84. Found: C, 31.20; H, 2.62; N, 9.76. ^{1}H-Nmr (300 MHz, DMSO-d_6) δ: 5.02-4.96 (m, unresolved, 2 H, Ar-CH_2-N), 3.87-3.75 (m, unresolved, 2 H, CH_2), 3.55-3.40 (m, unresolved, 2 H, CH_2), 3.30 (s, 6 H, CH_3).

6-Acetyl-1,4-bis(trifluoromethyl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyridazine (**6**)

To an ice-cooled solution of **1** (654 mg, 3 mmol) in dry dichloromethane (20 ml) was added dropwise a solution of 1-acetyl-1,2,5,6-tetrahydro-4-pyrrolidinopyridine[27] (620 mg, 3.2 mmol) in dry dichloromethane (5 ml), then the mixture was stirred at room temperature for 20 min under argon atmosphere. The volatile components were removed under reduced pressure and the residue was subjected to column chromatography (dichloromethane/methanol, 19:1). Recrystallization from diisopropyl ether/ethyl acetate afforded 695 mg (74%) of colorless crystals, mp 135-137°C. *Anal.* Calcd for $C_{11}H_9N_3OF_6$: C, 42.18; H, 2.90; N, 13.42. Found: C, 42.27; H, 2.95; N, 13.41. Ms: *m/z* (rel. int.) 314 (13%), 313 (M^+, 100), 294 (12), 271 (15), 270 (40), 256 (29), 202 (16), 174 (17). Ir (cm^{-1}): 1655 cm^{-1} (C=O). ^{1}H-Nmr (80 MHz, $CDCl_3$) δ: 5.20-4.70 (m, 2 H, Ar-CH_2-N), 4.10-3.70 (m, 2 H, CH_2), 3.30-3.00 (m, 2 H, CH_2), 2.21 (s, 3 H, CH_3).

1,4-Bis(trifluoromethyl)-5,6,7,8-tetrahydropyrido[3,4-*d*]pyridazine (**7**)

Compound (**6**) (220 mg, 0.7 mmol) was heated under reflux in 6 *N* hydrochloric acid (11 ml) for 1.5 h. After cooling, the solution was diluted with water (24 ml) and neutralized with saturated aqueous $NaHCO_3$. It was then exhaustively extracted with ether; the combined organic extracts were dried (Na_2SO_4) and evaporated. The residue was recrystallized from diisopropyl ether (deep-freeze) to give 175 mg (92%) of pale yellow crystals, mp 61-63°C, which slowly turned dark. *Anal.* Calcd for $C_9H_7N_3F_6$: C, 39.86; H, 2.60; N, 15.50. Found: C, 39.97; H, 2.60; N, 15.23. Ms: *m/z* (rel. int.) 272 (10%), 271 (M^+, 100), 270 (96), 268 (18), 252 (20), 174 (42), 145 (32), 107 (14), 75 (10), 69 (18), 57 (12), 51 (11). Ir (cm^{-1}): 3327 cm^{-1} (N-H). ^{1}H-Nmr (80 MHz, $CDCl_3$) δ: 4.24 (s, 2 H, Ar-CH_2-N), 3.40-2.90 (m, 4 H, Ar-CH_2-C, N-CH_2-C), 1.60 (s, 1 H, NH; exchangeable with D_2O).

1,4-Bis(trifluoromethyl)pyrido[3,4-*d*]pyridazine (**8**)

To a solution of **7** (135 mg, 0.5 mmol) in xylene (10 ml) was added 10% Pd/C catalyst (67 mg), and the mixture was heated under reflux for 24 h with vigorous stirring (completion of the reaction was controlled by tlc: dichloromethane/methanol, 9:1). The catalyst was filtered off and washed thoroughly with ethyl acetate. The combined solutions were evaporated under reduced pressure. The residue was purified by column chromatography (light petroleum/ethyl acetate, 4:1) and subsequent recrystallization from *n*-pentane (deep-freeze) to afford 101 mg (76%) of a pale yellow solid, mp 55-59°C. *Anal.* Calcd for $C_9H_3N_3F_6$: C, 40.47; H, 1.13; N, 15.73. Found: C, 40.25; H, 0.94; N, 15.93. Ms: *m/z* (rel. int.) 267 (M^+, 100%), 170 (22), 162 (13), 143 (15), 69 (21). ^{1}H-Nmr (80 MHz, $CDCl_3$) δ: 10.00-9.80 (m, 1 H, H-5), 9.31 (d, J = 5.9 Hz, 1 H, H-7), 8.16 (qd, $J_{7\text{-}8}$ = 5.9 Hz, $J_{H\text{-}F}$ = 1.5 Hz, 1 H, H-8).

Carrying out this reaction on a larger scale (starting from 3.2 g, 11.8 mmol of **7**) required longer reaction times (tlc monitoring, see above). When the process was stopped after 36 h, 1.20 g (38%) of the intermediate (**9**) (besides 1.1 g, 35%, of **8**) were isolated by column chromatography (dichloromethane/methanol, 19:1). Recrystallization from diisopropyl ether (deep-freeze) gave 1,4-bis(trifluoromethyl)-1,2-dihydropyrido[3,4-*d*]-pyridazine (**9**) as pale yellow crystals, mp 154-156°C. *Anal.* Calcd for $C_9H_5N_3F_6$: C, 40.16; H, 1.87; N, 15.61. Found: C, 40.37; H, 1.84; N, 15.46. Ms: *m/z* (rel. int.) 269 (M^+, 14%), 201 (10), 200 (100), 180 (15), 152 (17), 125 (11), 69 (11.). ^{1}H-Nmr (80 MHz, $CDCl_3$) δ: 8.83 (unresolved, 1H, H-5), overlapped by 8.76 (d, J = 4.9 Hz, 1 H, H-7), 7.26 (d, J = 4.9 Hz, 1 H, H-8; shows nOe on irradiation at 4.94 ppm), 7.15 (br s, 1 H, NH; exchangeable with D_2O), 4.94 (q, $J_{H\text{-}F}$ = 7.6 Hz, 1 H, H-1).

Cycloaddition Reaction of **8** with 1-Pyrrolidino-1-cyclopentene

A solution of **8** (133 mg, 0.5 mmol) and 1-pyrrolidino-1-cyclopentene[26] (274 mg, 2 mmol) in dry 1,4-dioxane (6 ml) was refluxed for 1 h under argon atmosphere. The volatile components were distilled off under reduced pressure. The residue was subjected to column chromatography (light petroleum/ethyl acetate, 9:1) to give 73 mg (48%) of 5,9-bis(trifluoromethyl)-7,8-dihydro-6*H*-cyclopent[*g*]isoquinoline (**10**) as a colorless solid, mp 78-82°. *Anal.* Calcd for $C_{14}H_9NF_6$: C, 55.09; H, 2.97; N, 4.59. Found: C, 54.78; H, 2.86; N, 4.53. Ms: *m/z* (rel. int.) 306 (16%), 305 (M^+, 100), 237 (15), 236 (79), 235 (15), 167 (31). ^{1}H-Nmr (80 MHz, $CDCl_3$) δ: 9.80-9.50 (m, 1 H, H-1), 8.66 (d, J = 6.0 Hz, 1 H, H-3), 8.20-7.80 (m, 1 H, H-4), 3.70-3.20 (m, 4 H, Ar-CH_2-C), 2.50-1.90 (m, 2 H, C-CH_2-C).

Cycloaddition Reaction of **8** with 1-Pyrrolidino-1-cycloheptene

A solution of **8** (267 mg, 1 mmol) and 1-pyrrolidino-1-cycloheptene[28] (660 mg, 4 mmol) in dry 1,4-dioxane (10 ml) was refluxed for 3 h under argon atmosphere. The volatile components were distilled off under reduced pressure. The residue was subjected to column chromatography (light petroleum/ethyl acetate, 9:1) to give 290 mg (72%) of a mixture (ratio: 2 : 3 or 3 : 2, respectively, according to ^{1}H-nmr) of 5,11-bis(trifluoromethyl)-7,8,9,10,10*a*,5*a*-hexahydro-10*a*-pyrrolidino-6*H*-cyclohept[*g*]isoquinoline and 5,11-bis(trifluoromethyl)-7,8,9,10,10*a*,5*a*-hexahydro-5*a*-pyrrolidino-6*H*-cyclohept[*g*]isoquinoline as a colorless oil. *Anal.* Calcd for $C_{20}H_{22}N_2F_6$: C, 59.40; H, 5.48; N, 6.93. Found: C, 59.49; H, 5.41; N, 6.81. Ms: *m/z* (rel. int.) 404 (M^+, 28%), 403 (10), 336 (18), 335 (100), 334 (20), 307 (18), 293 (13), 292 (65), 279 (32), 278 (29), 267 (14), 266 (70), 265 (10), 239 (10), 210 (21), 70 (57).

5,11-Bis(trifluoromethyl)-7,8,9,10-tetrahydro-6*H*-cyclohept[*g*]isoquinoline *N*-Oxide (**11**)

The isomer mixture (290 mg, 0.7 mmol) obtained as described above was dissolved in dichloromethane (20 ml). After addition of 50% *m*-chloroperbenzoic acid (345 mg, 1 mmol), the mixture was stirred at room temperature for 2 h, then it was diluted with dichloromethane (30 ml). The solution was washed successively with 0.5 *N* NaOH, water, and brine. The solvent was removed under reduced pressure and the residue was dissolved in 1-propanol (20 ml). Trifluoroacetic acid (3 ml, 39 mmol) was added, and the mixture was refluxed for 120 h. The volatile components were distilled off under reduced pressure and the residue was subjected to column chromatography (ethyl acetate). Recrystallization from methanol afforded 84 mg (33%) of yellow needles, mp 212-214°C. *Anal.* Calcd for $C_{16}H_{13}NOF_6$: C, 55.02; H, 3.75; N, 4.01. Found: C, 54.74; H, 3.48; N, 3.91. Ms: *m/z* (rel. int.) 349 (M^+, 45%), 334 (15), 333 (100), 304 (13), 291 (31), 279 (33), 264 (28), 236 (13), 235 (16), 210 (15). Ir (cm^{-1}): 1218 cm^{-1} (N-O). ^{1}H-Nmr (300 MHz, DMSO-d_6) δ: 8.86-8.82 (m, 1 H, H-1), 8.31 (dd, $J_{3\text{-}4}$ = 7.8 Hz, $J_{1\text{-}3}$ = 1.8 Hz, 1 H, H-3), 8.08 (qd, $J_{3\text{-}4}$ = 7.8 Hz, $J_{\text{H-F}}$ = 1.8 Hz, 1 H, H-4), 3.30-3.10 (m, 4 H, Ar-CH_2-C), 1.90-1.60 (m, 6 H, C-CH_2-C).

Cycloaddition Reaction of **8** with 1-Methyl-2-methylthio-2-pyrroline

A solution of **8** (267 mg, 1 mmol) and freshly prepared 1-methyl-2-methylthio-2-pyrroline[25] (516 mg, 4 mmol) in dry 1,4-dioxane (10 ml) was stirred at room temperature for 30 min under argon atmosphere. The volatile components were removed under reduced pressure. The residue was purified by short column chromatography (dichloromethane/ethyl acetate, 9:1), then the two components were separated by medium-pressure liquid chromatography (dichloromethane/ethyl acetate, 19:1). Evaporation of the first fraction gave 64 mg (20%) of

4,9-bis(trifluoromethyl)-2,3-dihydro-1-methyl-1*H*-pyrrolo[3,2-*g*]isoquinoline (**12b**) as a yellow solid, mp 104-115°C. *Anal.* Calcd for $C_{14}H_{10}N_2F_6$: C, 52.51; H, 3.15; N, 8.75. Found: C, 52.49; H, 2.88; N, 8.55. Ms: *m/z* (rel. int.) 321 (16%), 320 (M^+, 100), 319 (71), 250 (38). ^{1}H-Nmr (80 MHz, $CDCl_3$) δ: 9.27 (q, J_{H-F} = 2.4 Hz, 1 H, H-8), 8.39 (d, J = 5.9 Hz, 1 H, H-6), 7.80-7.60 (m, 1 H, H-5), 3.90-3.50 (m, 2 H, N-CH_2-C), overlapped by 3.60-3.20 (m, 2 H, Ar-CH_2-C), 3.12 (q, J_{H-F} = 3.3 Hz, 3 H, CH_3). Evaporation of the second fraction gave 144 mg (45%) of 4,9-bis(trifluoromethyl)-2,3-dihydro-1-methyl-1*H*-pyrrolo[2,3-*g*]isoquinoline (**12a**) as a yellow solid, mp 134-144°C. *Anal.* Calcd for $C_{14}H_{10}N_2F_6$: C, 52.51; H, 3.15; N, 8.75. Found: C, 52.48; H, 2.93; N, 8.64. Ms: *m/z* (rel. int.) 321 (16%), 320 (M^+, 100), 319 (94), 251 (12), 250 (39). ^{1}H-Nmr (80 MHz, $CDCl_3$) δ: 9.19 (q, J_{H-F} = 2.1 Hz, 1 H, H-5), 8.43 (d, J = 6.0 Hz, 1 H, H-7), 7.80-7.50 (m, 1 H, H-8), 3.90-3.60 (m, 2 H, N-CH_2-C), 3.60-3.20 (m, 2 H, Ar-CH_2-C), 3.13 (q, J_{H-F} = 3.4 Hz, 3 H, CH_3).

2,3-Dihydro-1,6-dimethyl-9-methoxycarbonyl-4-trifluoromethyl-1*H*-pyrrolo[2,3-*g*]isoquinolin-6-ium Perchlorate (**13**)

A solution of **12a** (110 mg, 0.34 mmol) and methyl iodide (1.42 g, 10 mmol) in tetrahydrofuran (10 ml) was stirred at room temperature for 16 h. The volatile components were removed under reduced pressure and the residue was taken up in methanol (10 ml). After addition of 70% perchloric acid (0.5 ml), the solution was refluxed for 5 min, then it was evaporated. The oily residue was triturated with little methanol and the solid thus obtained was recrystallized from methanol to give 70 mg (48%) of yellow needles, mp >220°C (decomp.). *Anal.* Calcd for $C_{16}H_{16}N_2O_6ClF_3$: C, 45.24; H, 3.80; N, 6.60. Found: C, 45.36; H, 3.71; N, 6.51. Ms: *m/z* (rel. int.) 325 (M^+, 50%), 324 (100), 323 (86), 322 (40), 256 (50), 255 (51). Ir (cm^{-1}): 1717 cm^{-1} (C=O). ^{1}H-Nmr (300 MHz, DMSO-d_6) δ: 8.99 (d, unresolved, 1 H, H-5; shows nOe on irradiation at 4.29 ppm), 8.37 (dd, J_{7-8} = 7.2 Hz, J_{5-7} = 1.2 Hz, 1 H, H-7; shows nOe on irradiation at 4.29 ppm), 7.89 (d, J_{7-8} = 7.2 Hz, 1 H, H-8), 4.29 (s, 3 H, N^+-CH_3), 4.02-3.92 (m, 5 H, OCH_3, N-CH_2-C), 3.55-3.44 (m, 2 H, Ar-CH_2-C), 3.32 (s, 3 H, NCH_3).

X-Ray Structure Determination of Compound **13**[29]

$C_{16}H_{16}N_2O_6ClF_3$, M_r = 427.76, orthorhombic, Pbca (No. 61), a = 21.957(4) Å, b = 19.195(4) Å, c = 8.466(2) Å, V = 3568(1) $Å^3$, Z = 8, D_C = 1.581 g cm^{-3}, μ = 0.277 mm^{-1}, F(000) = 1744, T = 24°C. A yellow prism (0.22 × 0.44 × 0.47 mm) was used for data collection (Philips PW1100 diffractometer, Mo Kα radiation, λ = 0.71069 Å). Of 3568 reflections collected (Θ-2Θ scans, Θ_{max} = 25°, correction for LP and absorption) 3132 were independent, and 1813 [$F > 6\sigma(F)$] were used for least-squares refinement after solving the structure with direct methods. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included in idealized

positions and refined with constraints. Effects caused by large thermal motion of the ClO_4 group were taken into account by introducing eight partially occupied oxygen positions with fixed coordinates. Final R = 0.036, wR = 0.038, and S = 1.37; final difference Fourier map showed minimum and maximum values of -0.19 and +0.17 e $Å^{-3}$. The programs SHELX76[30] and XTAL3.2[31] were used.

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