INVERSE-ELECTRON-DEMAND DIELS-ALDER REACTIONS OF CONDENSED PYRIDAZINES, 5.[1] 1,4-BIS(TRIFLUOROMETHYL)-PYRIDAZINO[4,5-*b*]INDOLE AS AN AZADIENE

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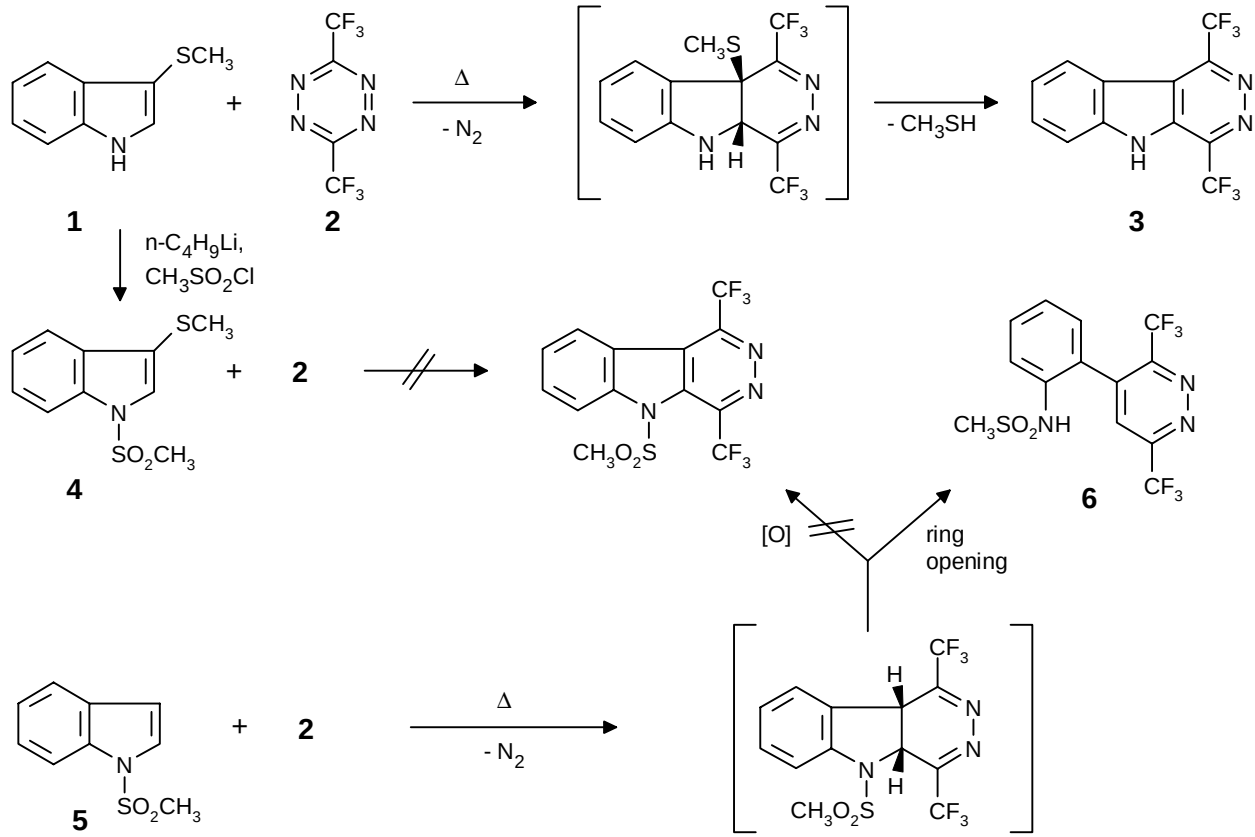
Abstract - The pyridazino[4,5-*b*]indole (**3**), which is conveniently available from 3-methylthioindole and the tetrazine (**2**), undergoes thermally induced inverse-electron-demand Diels-Alder reactions with enamines to afford the cycloalkene-annelated carbazoles (**7**,**8**) or the 2-substituted carbazole (**9**), respectively.

We have previously shown that 1,2-diazines annelated to a second π-electron-deficient aromatic ring (pyrido[3,4-*d*]pyridazines, pyridazino[4,5-*d*]pyridazines) can be successfully utilized as azadienes in inverse-electron-demand ($LUMO_{diene}$-controlled) Diels-Alder reactions.[1-4] There are also reports in the literature describing similar [4+2] cycloaddition reactions of pyridazines fused with a five-membered heterocycle (imidazo[4,5-*d*]pyridazines, 1,2,3-triazolo[4,5-*d*]pyridazines).[5,6] In the present paper, we wish to report a convenient synthesis of the title compound (**3**) and its reaction behavior on treatment with enamines as electron-rich C=C dienophiles.

The isolation of 1,4-bis(trifluoromethyl)pyridazino[4,5-*b*]indole (**3**) in 26% yield as a reaction product from a cycloaddition/cycloreversion process starting from indole and 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine[7] (**2**) has already been described by Seitz and Mohr.[8] As explained by the authors, the low yield results from partial consumption of the tetrazine component as an oxidant for a dihydropyridazino[4,5-*b*]indole intermediate. In order to elaborate a more efficient synthesis of **3**, we tried to overcome this problem by employing as a dienophile an indole derivative with an appropriate leaving group at C-3. Thus, the tetrazine (**2**) was reacted with an equimolar amount of readily available 3-methylthioindole[9,10] (**1**) in refluxing toluene to afford - after

spontaneous elimination of molecular nitrogen and methanethiol - the tricycle (**3**) in 58% yield (Scheme 1). As we were also interested in an access to a more electron-deficient derivative of **3**, we tried to introduce a methylsulfonyl substituent at N-5. However, treatment of **3** (or its anion, respectively) with methanesulfonyl chloride under various conditions did not effect any conversion. Moreover, an attempted [4+2] cycloaddition reaction of **2** with 1-methylsulfonyl-3-methylthioindole (**4**) (readily prepared from **1**) failed. On the other hand, we found that the tetrazine (**2**) slowly reacts with 1-methylsulfonylindole[11] (**5**) in refluxing toluene. Here, the product isolated in 26% yield turned out to be the 3,4,6-trisubstituted pyridazine (**6**). In this case, ring-opening of the intermediate dihydro tricycle obviously is the preferred rearomatization pathway, which is in accordance with previous observations with an analogous *N*-methyl compound.[8]

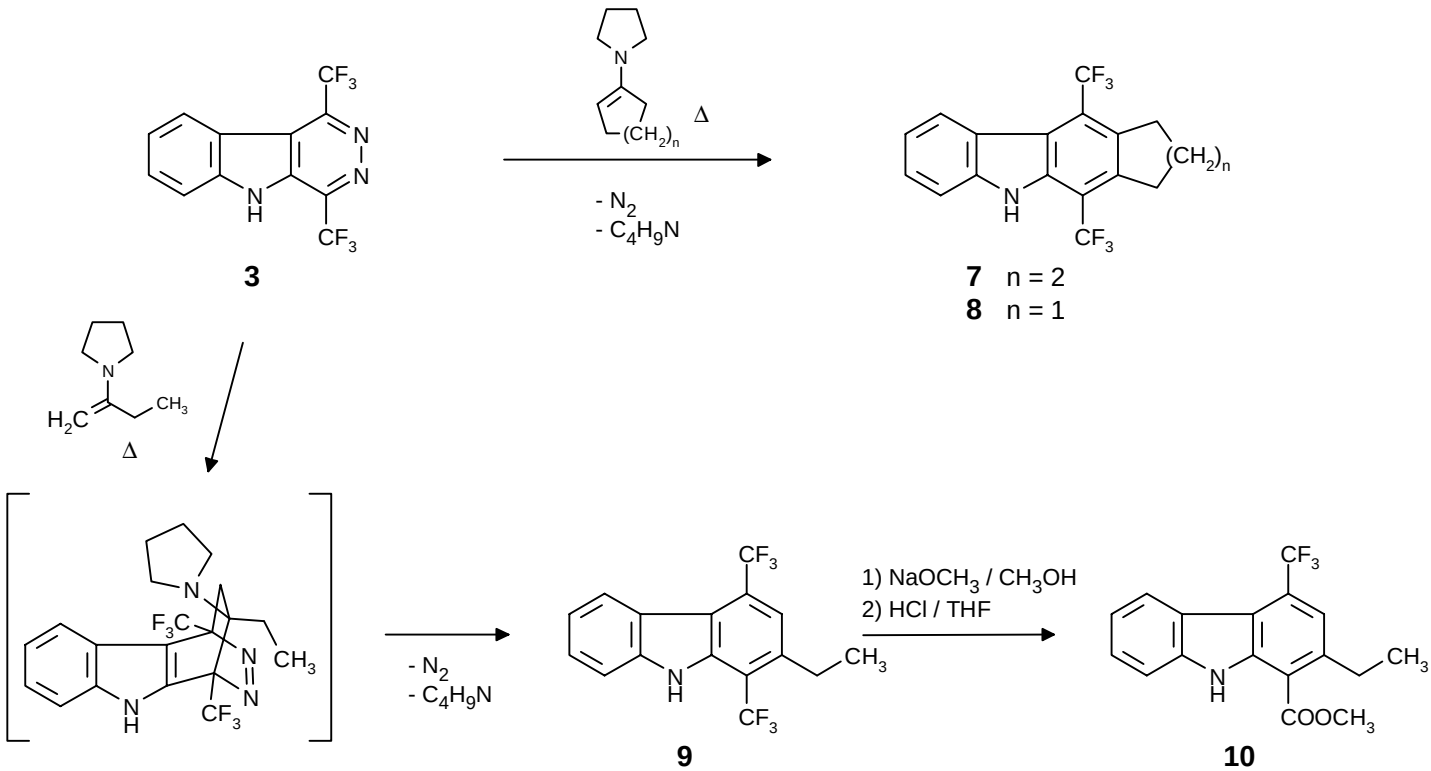
Scheme 1



Despite its relatively high LUMO energy (-1.80 eV, according to AM1[12] calculations which we carried out using the AMPAC software package[13]), compound (**3**) was found to react with the electron-rich dienophile, 1-pyrrolidino-1-cyclohexene, albeit at a low conversion rate: after 30 days of refluxing **3** with an excess of the enamine in 1,4-dioxane/acetonitrile, the expected tetracyclic product, 6,11-bis(trifluoromethyl)-7,8,9,10-tetra-hydrobenzo[*b*]carbazole (**7**) was isolated in 21% yield (Scheme 2). On the other hand, employment of the

corresponding enamine derived from *N*-methyl-4-piperidone (i.e. 1,2,5,6-tetrahydro-1-methyl-4-pyrrolidino-pyridine) did not effect any conversion even on prolonged refluxing; with 1-pyrrolidino-1-cycloheptene, only traces of a reaction product could be detected by glc/ms after 20 days. However, heating of the azadiene (**3**) with the more reactive five-membered enamine, 1-pyrrolidino-1-cyclopentene, in 1,4-dioxane solution for 5 days afforded (after chromatographic work-up) the cyclopenta[*b*]carbazole derivative (**8**) in 69% yield.

Scheme 2



Whereas the formation of the annelated carbazoles (**7**) and (**8**) does not permit any conclusion with respect to the preferred orientation of the azadiene (**3**) towards enamine-type dienophiles, employment of the acyclic enamine, 2-pyrrolidino-1-butene, was anticipated to shed some light on the regiochemistry of this [4+2] cyclo-addition process. Considering the different magnitudes of the LUMO p_z coefficients (as well as those of the partial charges) for the involved pyridazine carbon atoms (C-1 and C-4), which we obtained from an AM1[12] calculation, one may expect a higher affinity of the electron-rich enamine C-1 atom to pyridazine C-1 (p_z = 0.533; charge = -0.099) rather than to pyridazine C-4 (p_z = 0.458; charge = -0.197). Indeed, the product isolated in 68% yield after a reaction time of 6 days was found to be the 2-ethylcarbazole (**9**) as the sole isomer.[14] Compound (**9**) obviously results from loss of N_2 and pyrrolidine from an initially formed, strained cycloadduct as displayed in Scheme 2. Structural assignment with respect to the position of the ethyl substituent in **9** rests on selective transformation of one of the trifluoromethyl groups into a methyl ester

moiety: it is known that the susceptibility of a CF_3 group in an aromatic/heteroaromatic system towards nucleophilic attack or solvolysis under alkaline conditions is significantly increased by the presence of an N-H function in *ortho* or *para* position.[15,16] Thus, heating **9** with sodium methoxide/methanol in an autoclave afforded, after subsequent acidic hydrolysis of an intermediate ortho ester (in analogy to lit.[17]), the methyl ester (**10**) in 70% yield. In the ^{1}H-nmr spectrum of the latter compound, the CH_2 signal (quartet at δ = 3.19 ppm, J = 7.5 Hz) no longer shows the typical complex splitting pattern caused by H-F "through-space" coupling, as compared with the corresponding quartet of quartets (δ = 3.00 ppm, J_{H-H} = 7.5 Hz, J_{H-F} = 1.5 Hz) in compound (**9**). The position of the methoxycarbonyl function, in turn, unambiguously follows from nuclear Overhauser enhancement (nOe) observed for the N-H signal (and not for the H-5 doublet at 8.27 ppm) upon saturation of the OCH_3 resonance (see Experimental).

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 spectrophotometer; ^{1}H-nmr spectra were recorded on a Bruker AC 80 (80 MHz) and on a Varian UNITY*plus* 300 (300 MHz) spectrometer with TMS as internal reference (chemical shifts in δ ppm), the ^{13}C-nmr spectrum was recorded on a Bruker AM 400 (100 MHz, ^{13}C) instrument. Mass spectra were obtained on a Hewlett-Packard 5890A/5970B GC/MSD instrument. 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 (detection at 280 nm). Microanalyses were performed at the Institute of Physical Chemistry (Mag. J. Theiner, Microanalytical Laboratory), University of Vienna.

1,4-Bis(trifluoromethyl)pyridazino[4,5-*b*]indole[8] (**3**)

A solution of 3,6-bis(trifluoromethyl)-1,2,4,5-tetrazine[7] (436 mg, 2 mmol) and 3-methylthioindole[9,10] (326 mg, 2 mmol) in 10 ml of toluene (dried over molecular sieve, 4Å) was refluxed for 4 h. The solution was concentrated *in vacuo* to about half the volume and chilled; the precipitate was collected and washed with cold toluene. Recrystallization from acetonitrile gave 356 mg (58%) of colorless needles, mp 275°C (lit.,[8] 275°C). Ir, ^{1}H-nmr, and ms data were in agreement with those reported in the literature.[8]

1-Methylsulfonyl-3-methylthioindole (**4**)

To a solution of 3-methylthioindole[9,10] (2.445 g, 15 mmol) in 10 ml of dry tetrahydrofuran was added dropwise a 1.58 M solution of *n*-butyllithium in hexane (10.0 ml, 15.8 mmol) at -78°C under an atmosphere of

argon. The mixture was allowed to warm to 0°C for 1 h, then it was cooled again to -78°C. Methanesulfonyl chloride (1.890 g, 16.5 mmol) was added over a period of 20 min, then the solution was allowed to warm to room temperature during 16 h. It was then poured into 40 ml of 2% aqueous $NaHCO_3$ and extracted with ether. The organic layer was washed with 2% aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated. Purification by column chromatography (dichloromethane) afforded 3.053 g (85%) of colorless crystals, mp 72-75°C. *Anal.* Calcd for $C_{10}H_{11}NO_2S_2$: C, 49.77; H, 4.59; N, 5.80. Found: C, 50.03; H, 4.39; N, 5.66. Ms: *m/z* (rel. int.) 241 (49%, M^+), 163 (11), 162 (100), 128 (11), 120 (27), 118 (12). Ir (cm^{-1}): 1356, 1162 (SO). ^{1}H-Nmr (80 MHz, $CDCl_3$) δ: 2.48 (s, 3 H, SCH_3), 3.09 (s, 3 H, SO_2CH_3), 7.3-8.1 (m, 5 H, indole-H).

N-{2-[3,6-Bis(trifluoromethyl)pyridazin-4-yl]phenyl}methanesulfonamide (**6**)

A solution of 1-methylsulfonylindole[11] (**5**) (97 mg, 0.5 mmol) and the tetrazine (**2**) (109 mg, 0.5 mmol) in 3 ml of toluene (dried over molecular sieve, 4Å) was refluxed for 72 h. The mixture was allowed to cool, and the separated colorless crystals were collected and dried to give 50 mg (26%) of **6**, mp 210-223°C. *Anal.* Calcd for $C_{13}H_9N_3O_2F_6S$: C, 40.53; H, 2.35; N, 10.91. Found: C, 40.24; H, 2.20; N, 10.71. Ms: *m/z* (rel. int.) 386 (19%), 385 (100, M^+), 316 (33), 307 (12), 306 (20), 278 (40), 259 (10), 258 (40), 239 (12), 238 (74), 237 (30), 209 (18), 190 (21), 189 (26), 142 (23), 115 (10). Ir (cm^{-1}): 3197 (NH), 1338, 1149 (SO). ^{1}H-Nmr (80 MHz, DMSO-d_6) δ: 2.99 (s, 3 H, SO_2CH_3), 7.2-7.7 (m, 4 H, phenyl-H), 8.51 (s, 1 H, pyridazine H-5), 9.20 (br s, 1 H, NH). ^{13}C-Nmr (DMSO-d_6) δ: 152.4-151.2 (m, pyridazine C-3, C-6), 139.3, 135.1, 130.9, 130.1, 129.5, 127.1, 124.9, 123.3, 121.2 (q, $^1J_{C-F}$ = 276 Hz, CF_3), 121.0 (q, $^1J_{C-F}$ = 275 Hz, CF_3), 40.1 (SO_2CH_3).

6,11-Bis(trifluoromethyl)-7,8,9,10-tetrahydrobenzo[*b*]carbazole (**7**)

A solution of **3** (152 mg, 0.5 mmol) and 1-pyrrolidino-1-cyclohexene[18] (302 mg, 2 mmol) in 5 ml of dry 1,4-dioxane and 1 ml of dry acetonitrile was refluxed for 30 days under an atmosphere of argon. Every 72 h, another 2 mmol portion of enamine was added. The volatile components were removed *in vacuo* and the residue was subjected to column chromatography (light petroleum/ethyl acetate, 9:1) to afford 38 mg (21%) of **7** as colorless crystals, mp 88-91°C. *Anal.* Calcd for $C_{18}H_{13}NF_6$: C, 60.51; H, 3.67; N, 3.92. Found: C, 60.46; H, 3.89; N, 3.70. Ms: *m/z* (rel. int.) 358 (20%), 357 (100, M^+), 329 (28), 309 (15), 288 (20). ^{1}H-Nmr (80 MHz, $CDCl_3$) δ: 1.6-2.1 (m, 4 H, C-CH_2-C), 2.9-3.3 (m, 4 H, Ar-CH_2-C), 7.1-7.6 (m, 3 H, H-2, H-3, H-4), 8.32 (d, J = 8.1 Hz, H-1), 8.75 (br s, 1 H, NH).

4,10-Bis(trifluoromethyl)-2,3-dihydro-1*H*-cyclopenta[*b*]carbazole (**8**)

A solution of **3** (152 mg, 0.5 mmol) and 1-pyrrolidino-1-cyclopentene[18] (274 mg, 2 mmol) in 6 ml of dry 1,4-dioxane was refluxed for 5 days under an atmosphere of argon. After 72 h, another 2 mmol portion of enamine was added. The volatile components were removed *in vacuo* and the residue was subjected to column

chromatography (light petroleum/ethyl acetate, 9:1). Recrystallization from ethanol/water afforded 118 mg (69%) of **8** as colorless crystals, mp 131-133°C. *Anal.* Calcd for $C_{17}H_{11}NF_6$: C, 59.48; H, 3.23; N, 4.08. Found: C, 59.20; H, 3.27; N, 3.82. Ms: *m/z* (rel. int.) 344 (19%), 343 (100, M^+), 342 (13), 324 (12), 323 (25), 274 (18), 254 (12). ^{1}H-Nmr (80 MHz, $CDCl_3$) δ: 1.9-2.5 (m, 2 H, C-CH_2-C), 3.0-3.6 (m, 4 H, Ar-CH_2-C), 7.1-7.7 (m, 3 H, H-6, H-7, H-8), 8.31 (d, J = 7.6 Hz, 1 H, H-9), 8.65 (br s, 1 H, NH).

1,4-Bis(trifluoromethyl)-2-ethylcarbazole (**9**)

A solution of **3** (305 mg, 1 mmol) and 2-pyrrolidino-1-butene (500 mg, 4 mmol) (prepared using the method described in lit.[19]) in 13 ml of dry 1,4-dioxane was refluxed for 6 days under an atmosphere of argon. After 72 h, another 4 mmol portion of enamine was added. The volatile components were removed *in vacuo* and the residue was subjected to column chromatography (light petroleum/ethyl acetate, 9:1), followed by MPLC (light petroleum/ethyl acetate, 19:1). Recrystallization from *n*-pentane afforded 225 mg (68%) of **9** as colorless crystals, mp 95-97°C. *Anal.* Calcd for $C_{16}H_{11}NF_6$: C, 58.01; H, 3.35; N, 4.23. Found: C, 58.31; H, 3.22; N, 4.06. Ms: *m/z* (rel. int.) 332 (20%), 331 (100, M^+), 317 (17), 316 (89), 296 (18), 290 (10). ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 1.34 (t, J = 7.5 Hz, 3 H, $CH_2C\underline{H}_3$), 3.00 (qq, J = 7.5 Hz, 1.5 Hz, 2 H, $C\underline{H}_2CH_3$), 7.25-7.32 (m, 1 H, H-6), 7.44-7.52 (m, 3 H, H-3, H-7, H-8), 8.27 (d, J = 7.8 Hz, 1 H, H-5), 8.77 (br s, 1 H, NH).

Methyl 2-Ethyl-4-trifluoromethylcarbazole-1-carboxylate (**10**)

Sodium hydride (60% dispersion in mineral oil; 264 mg, 6.6 mmol) was added to 14 ml of absolute methanol with stirring. After addition of **9** (220 mg, 0.66 mmol), the mixture was heated in an autoclave to 160°C for 12 h, then it was partitioned between dichloromethane and water. The organic layer was evaporated *in vacuo* and the residue was taken up in 5 ml of tetrahydrofuran and 5 ml of 1.2 N hydrochloric acid. The solution was stirred at room temperature for 20 min, then it was cautiously neutralized by addition of aqueous ammonia. The mixture was diluted with 20 ml of water, then it was extracted with ether. The residue obtained on evaporation of the extract was subjected to MPLC (light petroleum/ethyl acetate, 19:1) to give 149 mg (70%) of **10** as colorless crystals, mp 105-107°C. *Anal.* Calcd for $C_{17}H_{14}NO_2F_3$: C, 63.55; H, 4.39; N, 4.36. Found: C, 63.43; H, 4.28; N, 4.32. Ms: *m/z* (rel. int.) 322 (10%), 321 (53, M^+), 290 (22), 289 (100), 261 (33). Ir (cm^{-1}): 3409 (NH), 1674 (CO). ^{1}H-Nmr (300 MHz, $CDCl_3$) δ: 1.33 (t, J = 7.5 Hz, 3 H, $CH_2C\underline{H}_3$; shows weak nOe on irradiation at 4.07 ppm), 3.19 (q, J = 7.5 Hz, 2 H, $C\underline{H}_2CH_3$), 4.07 (s, 3 H, OCH_3), 7.24-7.31 (m, 1 H, H-6), 7.42 (s, 1 H, H-3), 7.44-7.52 (m, 2 H, H-7, H-8), 8.27 (d, J = 8.1 Hz, 1 H, H-5), 10.17 (br s, 1 H, NH; shows nOe on irradiation at 4.07 ppm).

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