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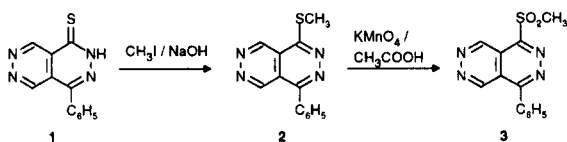
Starting from the thione **1**, a series of 1-(alkynyl-X)-4-phenylpyridazino[4,5-*d*]pyridazines **4-8** (X = O, NH, S) was prepared. Thermally induced intramolecular [4 + 2] cycloaddition reactions of the ethers **4**, **5** and the thioether **8** afforded *f*-annulated phthalazine derivatives.

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Inverse-electron-demand (LUMO_{diene}-controlled) Diels-Alder reactions of π -electron-poor *N*-heteroaromatics continue to attract considerable interest due to the wide applicability of this methodology for the synthesis of a large number of carbo- and heterocyclic systems by ring transformations [3]. As shown recently, pyridazines annelated to a second π -deficient *N*-heteroaromatic ring (another 1,2-diazine unit or a pyridine moiety) proved to be particularly useful aza-diene components in intermolecular [4 + 2] cycloaddition reactions, permitting the synthesis of a variety of condensed/substituted phthalazines and isoquinolines [4,5]. In extension of these investigations, we here report on the first examples of intramolecular [4 + 2] cycloaddition reactions of pyridazino[4,5-*d*]pyridazines with appropriate dienophilic side-chains.

For the introduction of alkynyl moieties of the general structure X-(CH₂)_n-C $\equiv$ CR (X = O, NH, S) [6-11] into position 1 of the pyridazino[4,5-*d*]pyridazine system, the thione **1** [12,13], which is conveniently available from 4-phenylpyridazino[4,5-*d*]pyridazin-1(2*H*)-one [12,14] was chosen as the key intermediate. Regioselective S-methylation of **1** with methyl iodide afforded the methylmercapto derivative **2** in good yield. This compound could be easily oxidized (using a method described for the synthesis of 1-methylsulfonyl-4-phenylphthalazine [15]) to the corresponding sulfone **3** with potassium permanganate in acetic acid solution.

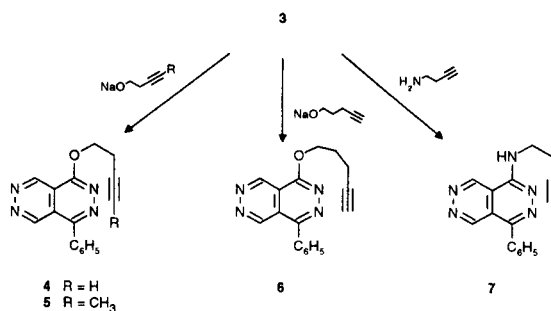
Scheme 1



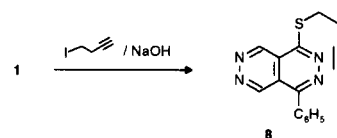
The required alkynyl ethers **4**, **5**, **6** were prepared in satisfactory yields by treatment of compound **3** at room temperature with the appropriate alcoholates, obtained from 3-butyne-1-ol, 3-pentyn-1-ol, and 4-pentyn-1-ol, respectively, in anhydrous tetrahydrofuran solution. Similarly, reaction of **3** with an excess of 4-amino-1-butyne [16] afforded the

butynylamino compound **7**. In order to prepare also a cycloaddition educt in which the side-chain and the aza-diene moiety are tethered by a sulfur atom (compound **8**), the thione **1** was reacted with 4-iodo-1-butyne [17] in alkaline medium. In contrast to the smooth S-methylation observed with **1**, the lower reactivity of 4-iodo-1-butyne required careful adjustment of the reaction conditions (see Experimental) to permit isolation of the thioether **8** in reasonable yields.

Scheme 2



Scheme 3

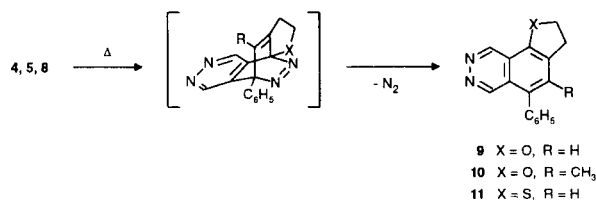


To investigate the ability of the butynyl ether **4** to undergo an intramolecular [4 + 2] cycloaddition, a solution of this compound in bromobenzene was heated to 150° under an argon atmosphere. Indeed, ¹H nmr monitoring indicated complete conversion of **4** into a new compound **9** after a reaction time of 36 hours. Most probably, the transformation proceeds *via* a strained, short-lived intermediate which spontaneously eliminates molecular nitrogen in a [4 + 2] cycloreversion step to afford the new furo[2,3-*f*]phthalazine **9** (isolated yield, 66%). It should be mentioned in this context that the monocyclic 1,2-diazine derivative, 6-(3-butyn-1-yloxy)-3-chloropyridazine, has been reported to give only traces of a cyclization product upon

heating in an inert solvent to $>200^\circ$ [6].

When the pentynyl ether **5** was subjected to the same conditions as described above (150° , bromobenzene solution), the observed conversion rate was considerably slower. Thus, a reaction time of 31 days was required for complete consumption of the starting material. While the terminal methyl group should provide a (slightly) activating electronic effect to the dienophilic $\text{C}\equiv\text{C}$ unit, this benefit is more than compensated by the steric hindrance of the reactive center. This overall effect of a terminal substituent on an acetylenic side-chain dienophile (which has been observed previously [6,11]) appears to be particularly relevant in the case of compound **5**, as there is a strong steric interaction between the methyl group and the phenyl substituent at C-4. The latter, in turn, is prevented from a coplanar orientation (with respect to the plane of the heteroaromatic system) by the steric requirements of H-5. This assumption is supported by force-field calculations [18] (indicating a torsion angle of 48.0°) as well as semiempirical AM1 calculations [19] (53.8° torsion between the two ring systems) which we carried out for compound **5**. However, it was found that cyclization of **5** into the corresponding furo[2,3-*f*]phthalazine derivative **10** can be accomplished in high yield (85%) within 4 days simply by employment of a higher-boiling solvent (1,2,4-trichlorobenzene) and a reaction temperature of 180° .

Scheme 4



In contrast to the successful transformations **4**→**9** and **5**→**10**, the 1-(4-pentyn-1-yloxy)-substituted pyridazino[4,5-*d*]pyridazine **6** did not show any cyclization tendency even upon prolonged heating at 200° (nitrobenzene as solvent). Here, only slow decomposition of the starting material was observed. Obviously, the insertion of one more methylene group into the spacer chain results in a drastic loss of entropic assistance which is critical for a [4 + 2] cycloaddition with an unactivated acetylene dienophile to take place. Similar observations have been described previously [6]. Also the butynylamino compound **7** was found to withstand attempted ring-closure, which in this case – in accordance with earlier findings [11,20] – has to be attributed to electronic reasons. Obviously, the pronounced electron-donating properties of the alkylamino group lead to a significant increase in the LUMO energy of the azadiene system and thus to a wider energy gap between the involved frontier orbitals [21].

Finally, heating of the thioether **8** in bromobenzene solution to 150° was found to effect intramolecular [4 + 2] cycloaddition (and subsequent loss of nitrogen) in a remarkably smooth manner. After a reaction time of only 2 hours, the conversion was complete to afford the new thieno[2,3-*f*]phthalazine derivative **11** in 54% yield (after chromatographic workup).

In summary, the described ring transformations of 1-(alkynyl-X)-substituted 4-phenylpyridazino[4,5-*d*]pyridazines (X = O, S) into *f*-annulated phthalazines have been shown to provide a convenient access to such fused systems. The analytical and spectroscopic data of all new compounds are in full agreement with the proposed structures. At present, the behavior of 4-substituted pyridazino[4,5-*d*]pyridazin-1(2*H*)-ones in intermolecular cycloaddition reactions with electron-rich dienophiles is under investigation.

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. The ir spectra were recorded for potassium bromide pellets on a Jasco IRA-1 spectrometer. The ^1H nmr spectra were obtained on a Bruker AC 80 (80 MHz) and on a Varian EM 390 (90 MHz) instrument (TMS as the internal reference). For tlc, Merck aluminium sheets pre-coated with Kieselgel 60 F₂₅₄ were used; column chromatography was carried out on Merck Kieselgel 60 (70-230 mesh).

1-Methylmercapto-4-phenylpyridazino[4,5-*d*]pyridazine (**2**).

To a solution of 240 mg (1 mmole) of 4-phenylpyridazino[4,5-*d*]pyridazine-1(2*H*)-thione (**1**) [12,13] in 10 ml of water and 2 ml of 2 *N* aqueous sodium hydroxide, 0.5 ml of methyl iodide were added and the mixture was stirred at room temperature for 1 hour. Then, 10 ml of water was added, and the suspension was extracted with dichloromethane. Evaporation of the extract, followed by recrystallization from ethyl acetate afforded 196 mg (77%) of yellow needles, mp $171\text{--}174^\circ$; ^1H nmr (deuteriochloroform): δ 9.91, 9.79 (each d, $J = 1.4$ Hz, H-5, H-8, 2 H), 7.86-7.57 (m, phenyl-H, 5 H), 2.94 (s, CH₃, 3 H); ir: 3060, 2920, 1560, 1480, 1440, 1380, 1270, 910, 760, 700 cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_{10}\text{N}_4\text{S}$: C, 61.40; H, 3.96; N, 22.03. Found: C, 61.69; H, 4.05; N, 21.85.

1-Methylsulfonyl-4-phenylpyridazino[4,5-*d*]pyridazine (**3**).

To a solution of 508 mg (2 mmoles) of **2** in 12 ml of glacial acetic acid was added gradually a 7% aqueous solution of potassium permanganate until the pink color persisted. Manganese dioxide was removed by addition of a 10% aqueous solution of sodium hydrogensulfite, then the mixture was diluted with water and the precipitate was collected, washed with water, and dried. Recrystallization from dry 1,4-dioxane gave 468 mg (82%) of yellow crystals, mp $200\text{--}201^\circ$; ^1H nmr (deuteriochloroform): δ 10.66, 9.99 (each d, $J = 1.5$ Hz, H-5, H-8, 2 H), 7.82-7.67 (m, phenyl-H, 5 H), 3.73 (s, CH₃, 3 H); ir: 3020, 2920, 1590, 1550, 1490, 1440, 1380, 1320, 1135, 960, 910, 760, 700 cm^{-1} .

Anal. Calcd. for $\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_2\text{S}$: C, 54.54; H, 3.52; N, 19.57. Found: C, 54.85; H, 3.62; N, 19.75.

1-(3-Butyn-1-yloxy)-4-phenylpyridazino[4,5-*d*]pyridazine (**4**).

To a stirred solution of 210 mg (3 mmol) of 3-butyn-1-ol in 5 ml of dry tetrahydrofuran were added 45 mg (1.5 mmol) of sodium hydride (80% suspension in paraffine). After 20 minutes, a suspension of 286 mg (1 mmol) of **3** in 25 ml of dry tetrahydrofuran was added, and the mixture was stirred for 2 hours. Dichloromethane (50 ml) was added, and the solution was washed several times with water, then it was dried and evaporated. Recrystallization from ethyl acetate afforded 173 mg (63%) of yellow crystals, mp 185-186°; ¹H nmr (deuteriochloroform): δ 10.03, 9.80 (each d, J = 1.5 Hz; H-5, H-8, 2 H), 7.76-7.57 (m, phenyl-H, 5 H), 4.94 (t, J = 6.6 Hz, OCH₂, 2 H), 2.93 (dt, J = 2.7, 6.6 Hz, CH₂-C≡, 2 H), 2.08 (t, J = 2.7 Hz, ≡CH, 1 H); ir: 3280, 3040, 2950, 1610, 1560, 1520, 1410, 1340, 1100, 1020, 820, 750, 690 cm⁻¹.

Anal. Calcd. for C₁₆H₁₂N₄O: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.31; H, 4.60; N, 19.98.

1-(3-Pentyn-1-yloxy)-4-phenylpyridazino[4,5-*d*]pyridazine (**5**).

To a stirred solution of 336 mg (4 mmol) of 3-pentyn-1-ol in 3 ml of dry tetrahydrofuran were added 60 mg (2 mmol) of sodium hydride (80% suspension in paraffine). After 30 minutes, a suspension of 286 mg (1 mmol) of **3** in 25 ml of dry tetrahydrofuran was added, and the mixture was stirred for 4 hours. Dichloromethane (50 ml) was added, and the solution was washed several times with water, then it was dried and evaporated. Column chromatography (eluting with dichloromethane/ethyl acetate, 4:1), followed by recrystallization from acetone afforded 92 mg (32%) of yellow needles, mp 128-130°; ¹H nmr (deuteriochloroform): δ 10.01, 9.78 (each d, J = 1.4 Hz; H-5, H-8, 2 H), 7.79-7.55 (m, phenyl-H, 5 H), 4.87 (t, J = 6.6 Hz, OCH₂, 2 H), 2.94-2.74 (m, CH₂-C≡, 2 H), 1.79 (t, J = 2.5 Hz, CH₃, 3 H); ir: 3050, 2960, 2920, 1590, 1510, 1420, 1330, 1000, 760, 700 cm⁻¹.

Anal. Calcd. for C₁₇H₁₄N₄O: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.57; H, 4.99; N, 19.34.

1-(4-Pentyn-1-yloxy)-4-phenylpyridazino[4,5-*d*]pyridazine (**6**).

To a stirred solution of 336 mg (4 mmol) of 4-pentyn-1-ol in 3 ml of dry tetrahydrofuran were added 60 mg (2 mmol) of sodium hydride (80% suspension in paraffine). After 30 minutes, a suspension of 286 mg (1 mmol) of **3** in 25 ml of dry tetrahydrofuran was added, and the mixture was stirred for 4 hours. Dichloromethane (50 ml) was added, and the solution was washed several times with water, then it was dried and evaporated. Column chromatography (eluting with dichloromethane/ethyl acetate, 9:1), followed by recrystallization from acetone afforded 98 mg (34%) of yellow needles, mp 134-136°; ¹H nmr (deuteriochloroform): δ 9.99, 9.79 (each d, J = 1.5 Hz; H-5, H-8, 2 H), 7.76-7.57 (m, phenyl-H, 5 H), 4.95 (t, J = 6.0 Hz, OCH₂, 2 H), 2.54-2.16 (m, CH₂-CH₂-C≡, 4 H), 2.01 (t, J = 2.4 Hz, ≡CH, 1 H); ir: 3250, 3040, 2950, 1590, 1500, 1420, 1360, 1330, 920, 900, 760, 680 cm⁻¹.

Anal. Calcd. for C₁₇H₁₄N₄O: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.38; H, 5.01; N, 19.16.

1-(3-Butyn-1-ylamino)-4-phenylpyridazino[4,5-*d*]pyridazine (**7**).

To a suspension of 286 mg (1 mmol) of **3** in 5 ml of dry tetrahydrofuran were added 414 mg (6 mmol) of 4-amino-1-butyne [16], and the mixture was stirred for 72 hours at 50°. The residue left after removal of the solvent was recrystallized from acetone to give 130 mg (47%) of yellow-brown needles, mp 168-172°; ¹H nmr (deuteriochloroform/deuterium oxide): δ 9.79, 9.73 (each d, J = 1.4 Hz; H-5, H-8, 2 H), 7.77-7.52 (m, phenyl-H, 5 H), 4.01 (t, J

= 6.3 Hz, NCH₂, 2 H), 2.76 (dt, J = 2.6, 6.3 Hz, CH₂-C≡, 2 H), 2.07 (t, J = 2.6 Hz, ≡CH, 1 H); ir: 3240, 3020, 2910, 1570, 1530, 1470, 1430, 1320, 1080, 920, 750, 680 cm⁻¹.

Anal. Calcd. for C₁₆H₁₃N₅: C, 69.80; H, 4.76; N, 25.44. Found: C, 69.59; H, 4.81; N, 25.15.

1-(3-Butyn-1-ylthio)-4-phenylpyridazino[4,5-*d*]pyridazine (**8**).

To a solution of 240 mg (1 mmol) of **1** in 10 ml of water and 2 ml of 2 *N* aqueous sodium hydroxide were added 180 mg (1 mmol) of 4-iodo-1-butyne [17], and the mixture was stirred at room temperature for 8 days; after 24 hours and 120 hours, additional 180 mg (1 mmol) portions of 4-iodo-1-butyne were added. The mixture was acidified (pH 3-4) with 2 *N* hydrochloric acid, then it was extracted with ethyl acetate. Evaporation of the organic layer, followed by recrystallization from methanol afforded 123 mg (42%) of yellow needles, mp 163-164°; ¹H nmr (deuteriochloroform): δ 9.93, 9.82 (each d, J = 1.4 Hz; H-5, H-8, 2 H), 7.85-7.59 (m, phenyl-H, 5 H), 3.78 (t, J = 6.7 Hz, SCH₂, 2 H), 2.87 (dt, J = 2.5, 6.7 Hz, CH₂-C≡, 2 H), 2.10 (t, J = 2.5 Hz, ≡CH, 1 H); ir: 3250, 3050, 2930, 1480, 1420, 1370, 1260, 1015, 910, 890, 760, 700 cm⁻¹.

Anal. Calcd. for C₁₆H₁₂N₄S: C, 65.73; H, 4.14; N, 19.16. Found: C, 65.98; H, 4.14; N, 19.44.

6,7-Dihydro-9-phenylfuro[2,3-*f*]phthalazine (**9**).

A solution of 276 mg (1 mmol) of **4** in 10 ml of bromobenzene was heated under an Ar atmosphere to 150° for 36 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography (eluting with ethyl acetate). Recrystallization from ethyl acetate gave 163 mg (66%) of pale yellow needles, mp 243-246°; ¹H nmr (deuteriochloroform): δ 9.58 (d, J = 1.5 Hz; H-4, 1 H), 9.45 (d, J = 1.5 Hz; H-1, 1 H), 7.69 (s, H-8, 1 H), 7.55-7.35 (m, phenyl-H, 5 H; shows nOe on irradiation at 9.45 ppm), 4.90 (t, J = 9.0 Hz, OCH₂, 2 H), 3.47 (t, J = 9.0 Hz, CCH₂, 2 H); ir: 3040, 2980, 2920, 1590, 1550, 1440, 1270, 1100, 920, 900, 760, 700 cm⁻¹.

Anal. Calcd. for C₁₆H₁₂N₂O: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.10; H, 5.00; N, 11.18.

6,7-Dihydro-8-methyl-9-phenylfuro[2,3-*f*]phthalazine (**10**).

A solution of 290 mg (1 mmol) of **5** in 10 ml of 1,2,4-trichlorobenzene was heated under an Ar atmosphere to 180° for 96 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography (eluting with dichloromethane/ethyl acetate, 1:1). Recrystallization from ethyl acetate gave 223 mg (85%) of pale yellow needles, mp 169-172°; ¹H nmr (deuteriochloroform): δ 9.53 (d, J = 1.4 Hz; H-4, 1 H), 9.01 (d, J = 1.4 Hz; H-1, 1 H), 7.60-7.40 (m, phenyl H-3', H-4', H-5', 3 H), 7.29-7.15 (m, phenyl H-2', H-6', 2 H; shows nOe on irradiation at 9.01 ppm), 4.92 (t, J = 9.0 Hz, OCH₂, 2 H), 3.41 (t, J = 9.0 Hz, CCH₂, 2 H), 2.23 (s, CH₃, 3 H); ir: 3040, 2980, 2920, 1580, 1440, 1420, 1360, 1310, 1260, 1080, 920, 760, 700 cm⁻¹.

Anal. Calcd. for C₁₇H₁₄N₂O: C, 77.84; H, 5.38; N, 10.68. Found: C, 77.88; H, 5.26; N, 10.60.

6,7-Dihydro-9-phenylthieno[2,3-*f*]phthalazine (**11**).

A solution of 292 mg (1 mmol) of **8** in 10 ml of bromobenzene was heated under an Ar atmosphere to 150° for 2 hours. The solvent was removed *in vacuo* and the residue was purified by column chromatography (eluting with ethyl acetate). Recrystallization from ethyl acetate gave 142 mg (54%) of pale yellow needles,

mp 182-184°; ¹H nmr (deuteriochloroform): δ 9.49, 9.43 (each d, J = 1.4 Hz, H-1, H-4, 2 H), 7.68 (s, H-8, 1 H), 7.60-7.45 (m, phenyl-H, 5 H), 3.70-3.55 (m, SCH₂CH₂, 4 H); ir: 3040, 2950, 1610, 1580, 1545, 1430, 1360, 1250, 910, 780, 715 cm⁻¹.

Anal. Calcd. for C₁₆H₁₂N₂S: C, 72.70; H, 4.58; N, 10.60. Found: C, 72.46; H, 4.81; N, 10.43.

REFERENCES AND NOTES

- [1] Counts as part **3** of the series 'Inverse-Electron-Demand Diels-Alder Reactions of Condensed Pyridazines'; for part **2** see ref [5].
- [2] Part of the Diploma Thesis of C. Loll, University of Vienna, Austria, 1993.
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- [21] Attempted conversion of **7** into a (presumably more reactive) *N*-acetyl derivative by treatment with acetic anhydride failed owing to resinification.