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STUDY OF THE REACTIVITY OF 5-ALKYNYL-4-CHLORO- AND 4-ALKYNYL-5-CHLOROPYRIDAZIN-3(2*H*)-ONES TOWARDS OXYGEN AND SULFUR NUCLEOPHILES

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Abstract - A study of the reactivity of 5-alkynyl-4-chloro- (**1a**,**b**) and 4-alkynyl-5-chloropyridazin-3(2*H*)-ones (**4a**,**b**) towards oxygen and sulfur nucleophiles ($NaOCH_3$, $NaSCH_3$, KOH and Na_2S) is reported. The synthesis of 5-alkynyl-2-methyl-4-methoxy- (**2a,b**) and 5-alkynyl-2-methyl-4-methylthiopyridazin-3(2*H*)-ones (**3a,b**) and their regioisomers 4-alkynyl-2-methyl-5-methoxy- (**5a**,**b**) and 4-alkynyl-2-methyl-5-methylthiopyridazin-3(2*H*)-ones (**6a**,**b**) is described, as well as the synthesis of 2-substituted 6-methylfuro[2,3-*d*]- (**7a,b,c**) and 2-substituted 6-methylthieno[2,3-*d*]pyridazin-7(6*H*)-ones (**8a,b**) and their regioisomers 2-substituted 5-methylfuro[2,3-*d*]- (**9a,b,c**) and 2-substituted 5-methylthieno[2,3-*d*]pyridazin-4(5*H*)-ones (**10a,b**).

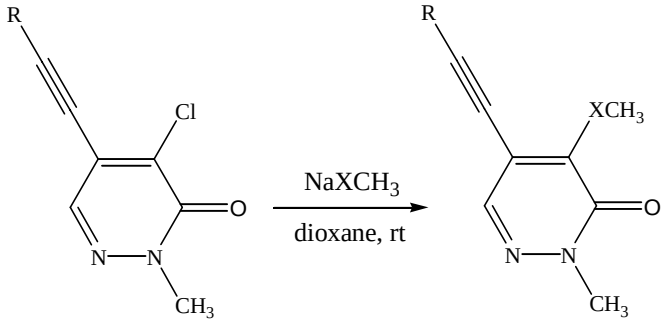
Recently, we described an efficient approach towards unsymmetrically disubstituted dialkynylpyridazin-3(2*H*)-ones.[1] The key step in their synthesis is the performance of a selective Sonogashira cross-coupling reaction on 4-chloro-2-methyl-5-trifluoromethanesulfonyloxypyridazin-3(2*H*)-one or its regioisomer, which allows the preparation of 5-alkynyl-4-chloro-2-methyl- and 4-alkynyl-5-chloro-2-methylpyridazin-3(2*H*)-ones respectively.[1] These monoalkynylated pyridazinones are useful intermediates for the synthesis of new pyridazinone based compounds.[2] They allow the performance of a second palladium-catalysed cross-coupling reaction (Sonogashira or Suzuki reaction) as described earlier,[1] but should also permit a wide variety of other reactions on the chlorinated carbon atom as well as on the triple bond. In this paper, we present the reactivity of 5-alkynyl-4-chloro-2-methyl- and 4-alkynyl-5-chloro-2-methylpyridazin-

3(2*H*)-ones towards oxygen and sulfur nucleophiles, resulting in the formation of alkoxy- and alkylthioalkynylpyridazinones (**2**, **3**, **5** and **6**) as well as bicyclic furo- and thienopyridazinones (**7**-**10**).

In a previous paper, we described Suzuki arylations on 4-chloro-5-methoxy-2-methylpyridazin-3(2*H*)-one and its regioisomer 5-chloro-4-methoxy-2-methylpyridazin-3(2*H*)-one using $Pd(PPh_3)_4$ as the catalyst.[3,4] Similarly, a direct Sonogashira alkynylation of these chloromethoxypyridazinones would be the shortest way to synthesize compounds of type **2** and **5.** However, attempts to perform a Sonogashira cross-coupling reaction with phenylacetylene using $Pd(PPh_3)_2Cl_2$ as precatalyst were unsuccessful, and gave only traces of the desired compounds. Trials to use Et_3N both as base and as the solvent, or to change the solvent from THF to DMF, for the alkynylation of 4-chloro-5-methoxy-2-methylpyridazin-3(2*H*)-one were all in vain. Also, other palladium catalysts ($Pd(PPh_3)_4$ and $Pd(dppf)Cl_2$) were used in hope to obtain 5-methoxy-2-methyl-4-phenylethynylpyridazin-3(2*H*)-one (**5a**), however, no satisfactory results were achieved.

These negative results prompted us to examine nucleophilic substitution reactions on the chlorinated carbon atom in C-4 or C-5 position of the 5-alkynyl-4-chloro-2-methyl- (**1a,b**) and 4-alkynyl-5-chloro-2-methylpyridazin-3(2*H*)-ones (**4a,b**) respectively using CH_3O^- and CH_3S^- as the nucleophiles. When reacting **1a,b** with $NaOCH_3$ and $NaSCH_3$ in dioxane at room temperature, 5-alkynyl-2-methyl-4-methoxy- (**2a,b**) and 5-alkynyl-4-methylthio-2-methylpyridazin-3(2*H*)-ones (**3a,b**) respectively were successfully obtained in moderate to good yields (Table 1).

Table 1: Nucleophilic substitution reactions of compounds (**1a,b**).



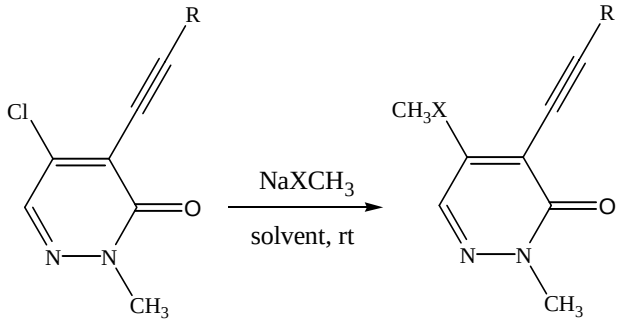
1a,b **2a,b or 3a,b**

Product	R	X	Reaction time (h)	Yield (%)
2a	C_6H_5	O	2	55[a]
2b	C_3H_7	O	2	57[a]
3a	C_6H_5	S	2	70[b]
3b	C_3H_7	S	19	90[b]

[a]Reaction conditions: **1a** or **1b** (1 mmol); 4.86 M $NaOCH_3$ (1.07 mmol); dioxane (4.3 mL) at room temperature.
[b]Reaction conditions: **1a** or **1b** (1 mmol); $NaSCH_3$ (1.6 mmol); dioxane (5.5 mL) at room temperature.

When the 4-alkynyl-5-chloro-2-methylpyridazin-3(2*H*)-ones (**4a,b**) were subjected to identical nucleophilic substitution conditions ($NaOCH_3$ or $NaSCH_3$ in dioxane), only 5-methoxy-2-methyl-4-phenylethynylpyridazin-3(2*H*)-one (**5a**) was obtained in good yield (Table 2). The reaction of **4a** with $NaSCH_3$ and **4b** with $NaOCH_3$ or $NaSCH_3$ in dioxane gave a mixture of products due to nucleophilic addition on the triple bond (as shown by MS, ^{1}H-NMR and ^{13}C-NMR spectra).[5] To overcome this problem, dioxane was replaced by methanol, which is known to favor nucleophilic attack in C-5 over C-4 position in the case of 2-substituted 4,5-dichloropyridazin-3(2*H*)-ones.[6] In this way, compounds (**5b**) and (**6a,b**) were obtained (Table 2).

Table 2: Nucleophilic substitution reactions of compounds (**4a,b**).



4a,b **5a,b or 6a,b**

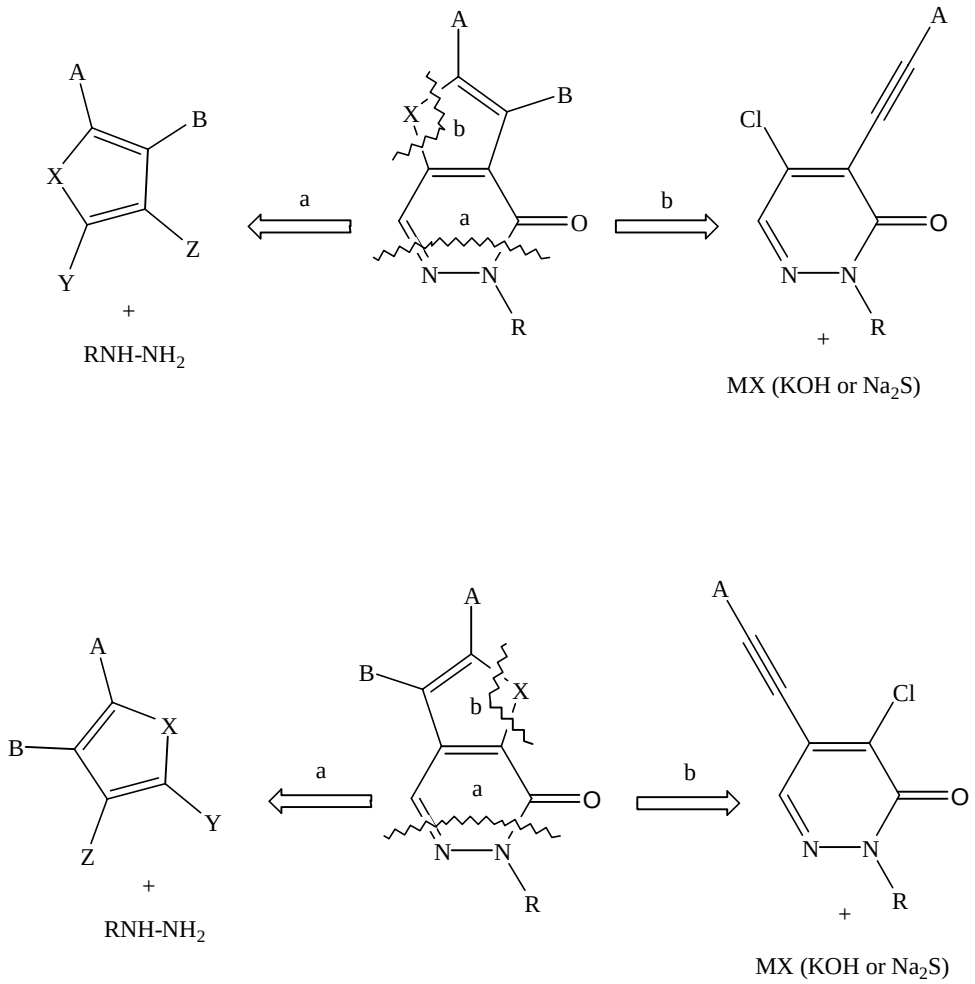
Product	R	X	Solvent	Reaction time (h)	Yield (%)
5a	C_6H_5	O	dioxane	2	90[a]
5b	C_3H_7	O	methanol	10	36[a,b]
6a	C_6H_5	S	methanol	3	90[c]
6b	C_3H_7	S	methanol	1.5	38[b,c]

[a]Reaction conditions: **4a** or **4b** (1 mmol); 4.86 M $NaOCH_3$ (1.07 mmol); solvent (4.3 mL) at room temperature.
[b]No starting material was recovered.
[c]Reaction conditions: **4a** or **4b** (1 mmol); $NaSCH_3$ (1.6 mmol); methanol (5.5 mL) at room temperature.

Furthermore, encouraged by the reported biological activities of the furo- and thienopyridazine and pyridazinone derivatives,[7] we examined the preparation of 2-substituted 6-methylfuro[2,3-*d*]- (**7a,b,c**) and 2-substituted 6-methylthieno[2,3-*d*]pyridazin-7(6*H*)-ones (**8a,b**) and their regioisomers 2-substituted 5-methylfuro[2,3-*d*]- (**9a,b,c**) and 2-substituted 5-methylthieno[2,3-*d*]pyridazin-4(5*H*)-ones (**10a,b**). In the earliest reports, the preparation of these fused compounds was based on the reaction of a hydrazine with a 2,3-dicarbonylated furan or thiophene to form the pyridazine moiety (Figure 1, way a).[8] We now report a different and smooth method, based on the reaction of an *ortho*-alkynyl-chloropyridazin-3(2*H*)-one with KOH or Na_2S (Figure 1, way b). The mechanism of these ring closure reactions, can be

considered as a nucleophilic addition reaction on the triple bond of the alkynyl-chloropyridazin-3(2*H*)-ones with a hydroxide or sulfide anion, followed by an intramolecular nucleophilic substitution,[9] or the opposite,[10] or the two mechanisms may occur simultaneously. The choice of different alkynyl groups in the selective Sonogashira cross-coupling reaction permits the introduction of the desired substituent at the C-2 position of the furo[2,3-*d*]- and thieno[2,3-*d*]pyridazinones. The retrosynthetic analysis of our new (way b) and the literature pathways (way a), shows the difference between the two methodologies (Figure 1).

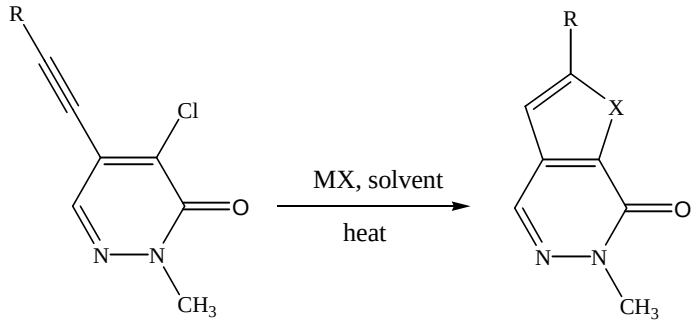
Figure 1: Retrosynthetic analysis of the literature and the new pathway of ring closure reactions.



Treatment of 5-alkynyl-4-chloro-2-methyl- (**1a,b**) and 4-alkynyl-5-chloro-2-methylpyridazin-3(2*H*)-ones (**4a,b**) with an aqueous solution of KOH in dioxane[9b] yielded 2-substituted 6-methylfuro[2,3-*d*]pyridazin-

7(6*H*)-ones (**7a,b**) and 2-substituted 5-methylfuro[2,3-*d*]pyridazin-4(5*H*)-ones (**9a,b**) respectively (Tables 3 and 4). The very low yield of the compounds (**7b**) and (**9b**) (Tables 3 and 4) was assumed to be due to the acidity of the protons in the C-3′ position of the pentynyl group of **1b** and **4b**. To examine this assumption, we prepared 4-chloro-2-methyl-5-*tert*-butylethynyl- (**1c**) and 5-chloro-2-methyl-4-*tert*-butylethynylpyridazin-3(2*H*)-one (**4c**).[1] Subsequent treatment of **1c** and **4c** with an aqueous solution of KOH in dioxane led to the formation of 6-methyl-2-*tert*-butylfuro[2,3-*d*]pyridazin-7(6*H*)-one (**7c**) and 5-methyl-2-*tert*-butylfuro[2,3-*d*]pyridazin-4(5*H*)-one (**9c**) in 65 % and 52 % yields respectively (Tables 3 and 4). These observations support the idea that the acidity of the propargylic protons indeed is responsible for the failure to cyclise **1b** and **4b**.

Table 3: Ring closure reactions of compounds (**1a**,**b**,**c**).



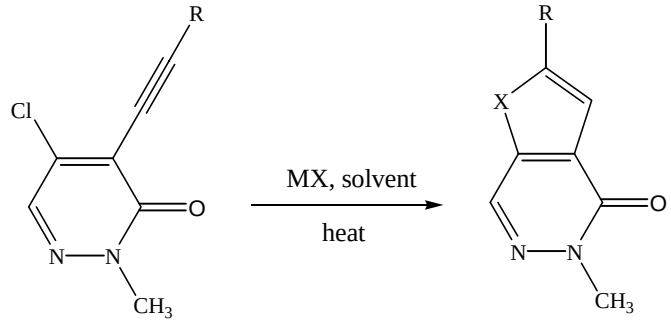
1a,b,c **7a,b,c or 8a,b**

Product	R	X (MX)	Solvent	Temperature	Reaction time (h)	Yield (%)
7a	C_6H_5	O (KOH)	dioxane	100°C	4	80[a]
7b	C_3H_7	O (KOH)	dioxane	100°C	2	4[a,b]
7c	$C(CH_3)_3$	O (KOH)	dioxane	100°C	20	65[a]
8a	C_6H_5	S (Na_2S)	DMF	60°C	0.75	72[c]
8b	C_3H_7	S (Na_2S)	DMF	60°C	0.75	60[c]

[a]Reaction conditions: **1a** or **1b** or **1c** (1 mmol); KOH (13 mmol); H_2O (4.6 mL); dioxane (9 mL) at 100°C.
[b]No starting material was recovered.
[c]Reaction conditions: **1a** or **1b** (1 mmol); ($Na_2S.9H_2O$) (2.2 mmol); DMF (4.6 mL) at 60°C.

Similarly, by reacting 5-alkynyl-4-chloro-2-methyl- (**1a,b**) and 4-alkynyl-5-chloro-2-methylpyridazin-3(2*H*)-ones (**4a,b**) with sodium sulfide ($Na_2S.9H_2O$) in DMF, the expected ring closure reactions occurred providing 2-substituted 6-methylthieno[2,3-*d*]pyridazin-7(6*H*)-ones (**8a,b**) and 2-substituted 5-methylthieno[2,3-*d*]pyridazin-4(5*H*)-ones (**10a,b**) (Tables 3 and 4).[9b]

Table 4: Ring closure reactions of compounds (**4a**,**b**,**c**).



4a,b,c **9a,b,c or 10a,b**

Product	R	X (MX)	Solvent	Temperature	Reaction time (h)	Yield (%)
9a	C_6H_5	O (KOH)	dioxane	100°C	10	50[a]
9b	C_3H_7	O (KOH)	dioxane	100°C	20	3[a,b]
9c	$C(CH_3)_3$	O (KOH)	dioxane	100°C	13	52[a]
10a	C_6H_5	S (Na_2S)	DMF	60°C	0.75	79[c]
10b	C_3H_7	S (Na_2S)	DMF	60°C	0.50	19[b,c]

[a]Reaction conditions: **4a** or **4b** or **4c** (1 mmol); KOH (13 mmol); H_2O (4.6 mL); dioxane (9 mL) at 100°C.
[b]No starting material was recovered.
[c]Reaction conditions: **4a** or **4b** (1 mmol); ($Na_2S.9H_2O$) (2.2 mmol); DMF (4.6 mL) at 60°C.

In conclusion, by performing nucleophilic substitution reactions on alkynyl-chloropyridazinones with alkoxides and alkylthiolates, alkoxy-alkynyl- and alkylthio-alkynylpyridazinones were easily prepared. Moreover, starting from the same starting materials, reactions with hydroxide and sulfide anions yielded bicyclic furo[2,3-*d*]- and thieno[2,3-*d*]pyridazinones respectively.

EXPERIMENTAL

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Unity 400 spectrometer in $CDCl_3$ with TMS as the internal standard. Chemical shifts are given in ppm and *J* values in Hz. The multiplicity of the signals is indicated by the following abbreviations: s singlet, d doublet, t triplet, q quadruplet, h hexaplet and m multiplet. HRMS and product ion spectra were recorded on a quadrupole-time of flight mass spectrometer (QTof 2, Micromass, Manchester, UK) equipped with a standard electrospray ionisation (ESI) interface. Samples were dissolved in CH_3OH containing 0.1 % formic acid and diluted to a concentration of approximately 10^{-5} mol/L. 1µL injections were directed to the mass spectrometer at a flow rate of 5µL/min CH_3OH (0.1% formic acid), using the CapLC HPLC system (Waters, Millford).

Product ion spectra were recorded selecting the protonated molecule $[M+H]^+$ in the quadrupole. This precursor ion is fragmented in the collision cell using Ar as collision gas and a collision energy of 20, 25 and 30 eV. IR spectra were obtained as potassium bromide pellets with a Brucker Vector 22 spectrometer. Melting points were recorded using a Büchi B-545 apparatus and are uncorrected. All reagents were purchased from commercial sources (Acros, Aldrich) and were used as such. Dioxane 99+ % (Acros) was dried over sodium/benzophenone and freshly distilled before use. DMF 99.9 % (Acros) was used as such. Flash column chromatography was performed on Kiesel gel 60 (Merck), 0.040-0.063 mm.

General procedure for the preparation of the 5-alkynyl-2-methyl-4-methoxy- (2a,b) and the 4-alkynyl-2-methyl-5-methoxypyridazin-3(2*H*)-ones (5a,b):

To a solution of 5-alkynyl-4-chloro- (**1a,b**) or 4-alkynyl-5-chloro-2-methylpyridazin-3(2*H*)-ones (**4a,b**) (1 mmol) in dioxane (4.3 mL) a 4.86 M $NaOCH_3$ solution (0.22 mL, 1.07 mmol) was added. The reaction mixture was stirred at rt (the flask was equipped with a drying tube) until total consumption of the starting material (TLC analysis and/or DCI-MS). The mixture was then poured into water (60 mL) and extracted with EtOAc (3x75 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure. The residue was purified by column chromatography when indicated.

4-Methoxy-2-methyl-5-phenylethynylpyridazin-3(2*H*)-one (2a). No column chromatography was performed. Yield 55%; pale brown solid; mp 65.3°C (Hexane/Petroleum ether); δ_H ($CDCl_3$): 7.67 (s, 1H, H-6), 7.55-7.50 (m, 2H, H_{Ph}-2,6), 7.42-7.35 (m, 3H, H_{Ph}-3,4,5), 4.41 (s, 3H, OCH_3), 3.76 (s, 3H, NCH_3); δ_C ($CDCl_3$): 157.26 (C-3), 155.15 (C-4), 138.64 (C-6), 131.69 (C_{Ph}-2,6), 129.45 (C_{Ph}-4), 128.57 (C_{Ph}-3,5), 122.04 (C_{Ph}-1), 109.59 (C-5), 99.19 (C-2"), 81.11 (C-1"), 60.49 (OCH_3), 40.03 (NCH_3); ν_{max} (KBr): 2925, 2854, 2214, 1654, 1606, 1525, 1334, 1007, 759, 691, 528 cm^{-1}; MS (ESI) m/z: 241 (100%), 197, 142, 115, 91; HRMS (ESI) for $C_{14}H_{13}N_2O_2$ $[M+H]^+$: calcd 241.0977, found 241.0975; Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 70.06; H, 4.99; N, 11.76.

4-Methoxy-2-methyl-5-(pent-1-ynyl)pyridazin-3(2*H*)-one (2b). No column chromatography was performed. Yield 57%; brownish oil; δ_H ($CDCl_3$): 7.55 (s, 1H, H-6), 4.31 (s, 3H, OCH_3), 3.73 (s, 3H, NCH_3), 2.43 (t, *J* = 7.0 Hz, 2H, H-3"), 1.64 (h, *J* = 7.3 Hz, 2H, H-4"), 1.04 (t, *J* = 7.3 Hz, 3H, H-5"); δ_C ($CDCl_3$): 157.48 (C-3), 155.13 (C-4), 139.26 (C-6), 110.73 (C-5), 101.50 (C-2"), 72.81 (C-1"), 60.27 (OCH_3), 39.94 (NCH_3), 21.80, 21.79 (C-3" or C-4"), 13.50 (C-5"); ν_{max} (liquid film): 2964, 2936, 2873, 2229, 1651, 1597, 1457, 1311, 1051, 1004, 923, 783, 647 cm^{-1}; MS (ESI) m/z: 207, 177, 164, 151 (100%); HRMS (ESI) for $C_{11}H_{15}N_2O_2$ $[M+H]^+$: calcd 207.1134, found 207.1137; Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 64.13; H, 6.81; N, 13.47.

5-Methoxy-2-methyl-4-phenylethynylpyridazin-3(2*H*)-one (5a). No column chromatography was performed. Yield 90%; pale brown solid; mp 116.2°C (Ethanol); δ_H ($CDCl_3$): 7.74 (s, 1H, H-6), 7.61-7.55 (m, 2H, H_{Ph}-2,6), 7.36-7.32 (m, 3H, H_{Ph}-3,4,5), 4.12 (s, 3H, OCH_3), 3.79 (s, 3H, NCH_3); δ_C ($CDCl_3$): 160.97, 159.63 (C-5 or C-3), 131.93 (C_{Ph}-2,6), 128.95 (C_{Ph}-4), 128.31 (C_{Ph}-3,5), 127.34 (C-6), 122.87 (C_{Ph}-1), 106.01 (C-2'), 102.84 (C-4), 79.99 (C-1'), 57.77 (OCH_3), 40.35 (NCH_3); ν_{max} (KBr): 2957, 2925, 2854, 2204, 1635, 1345, 1284, 1177, 1124, 968, 760, 694, 529, 481 cm^{-1}; MS (ESI) m/z: 241, 226, 199, 143, 102 (100%); HRMS (ESI) for $C_{14}H_{13}N_2O_2$ $[M+H]^+$: calcd 241.0977, found 241.0975; Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 69.99; H, 5.03; N, 11.66. Found: C, 69.90; H, 5.13; N, 11.70.

5-Methoxy-2-methyl-4-(pent-1-ynyl)pyridazin-3(2*H*)-one (5b). This compound was prepared using the general procedure, but instead of dioxane MeOH has been used as the solvent. Chromatography eluent: Hexane/EtOAc 4:6; Yield 36%; pale yellow solid; mp 107.6°C (Hexane/Petroleum ether); δ_H ($CDCl_3$): 7.69 (s, 1H, H-6), 4.06 (s, 3H, OCH_3), 3.76 (s, 3H, NCH_3), 2.51 (t, *J* = 7.2 Hz, 2H, H-3'), 1.66 (h, *J* = 7.3 Hz, 2H, H-4'), 1.06 (t, *J* = 7.3 Hz, 3H, H-5'); δ_C ($CDCl_3$): 167.08, 159.62 (C-5 or C-3), 127.35 (C-6), 106.68, 105.23 (C-2' or C-4), 71.28 (C-1′), 57.63 (OCH_3), 40.29 (NCH_3), 22.25, 21.96 (C-3′ or C-4′), 13.52 (C-5′); ν_{max} (KBr): 2964, 2932, 2226, 1629, 1586, 1336, 1283, 1249, 1158, 1005, 958, 890, 755, 493; MS (ESI) m/z: 207, 163, 153, 123 (100%); HRMS (ESI) for $C_{11}H_{15}N_2O_2$ $[M+H]^+$: calcd 207.1134, found 207.1133; Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.97; H, 6.92; N, 13.50.

General procedure for the preparation of the 5-alkynyl-2-methyl-4-methylthio- (3a,b) and the 4-alkynyl-2-methyl-5-methylthiopyridazin-3(2*H*)-ones (6a,b):

To a solution of 5-alkynyl-4-chloro- (**1a,b**) or 4-alkynyl-5-chloro-2-methylpyridazin-3(2*H*)-ones (**4a,b**) (1 mmol) in dioxane (5.5 mL) $NaSCH_3$ (0.11 g, 1.6 mmol) was added. The reaction mixture was stirred at rt (the flask was equipped with a drying tube) until total consumption of the starting material (TLC analysis and/or DCI-MS). The reaction mixture was then poured into water (70 mL) and extracted with EtOAc (3x85 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure. The residue was purified by column chromatography when indicated.

4-Methylthio-2-methyl-5-phenylethynylpyridazin-3(2*H*)-one (3a). Chromatography eluent: Heptane/ Ether 1:1; Yield 70%; yellowish solid; mp 95.2°C (Ethanol); δ_H ($CDCl_3$): 7.64 (s, 1H, H-6), 7.58-7.53 (m, 2H, H_{Ph}-2,6), 7.44-7.36 (m, 3H, H_{Ph}-3,4,5), 3.76 (s, 3H, NCH_3), 2.85 (s, 3H, SCH_3); δ_C ($CDCl_3$): 158.65 (C-3), 142.63 (C-4), 137.22 (C-6), 131.77 (C_{Ph}-2,6), 129.75 (C_{Ph}-4), 128.63 (C_{Ph}-3,5), 123.12 (C-5),

121.78 (C_{Ph}-1), 102.45 (C-2''), 83.29 (C-1''), 40.36 (NCH_3), 16.33 (SCH_3); ν_{max} (KBr): 2927, 2203, 1626, 1492, 1371, 1249, 1047, 860, 758, 692, 535 cm^{-1}; MS (ESI) m/z: 257, 214, 200 (100%), 167, 129; HRMS (ESI) for $C_{14}H_{13}N_2OS$ $[M+H]^+$: calcd 257.0749, found 257.0739; Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.53; H, 4.82; N, 11.12.

4-Methylthio-2-methyl-5-(pent-1-ynyl)pyridazin-3(2*H*)-one (3b). No column chromatography was performed. Yield 90%; brownish oil; δ_H ($CDCl_3$): 7.52 (s, 1H, H-6), 3.73 (s, 3H, NCH_3), 2.77 (s, 3H, SCH_3), 2.48 (t, *J* = 7.0 Hz, 2H, H-3''), 1.66 (h, *J* = 7.3 Hz, 2H, H-4''), 1.06 (t, *J* = 7.3 Hz, 3H, H-5''); δ_C ($CDCl_3$): 158.86 (C-3), 141.89 (C-4), 137.69 (C-6), 124.30 (C-5), 105.28 (C-2''), 75.28 (C-1''), 40.32 (NCH_3), 21.93, 21.73 (C-3'' or C-4''), 16.22 (SCH_3), 13.56 (C-5''); ν_{max} (liquid film): 2929, 2856, 2226, 1732, 1643, 1488, 1370, 1145, 861, 778, 690 cm^{-1}; MS (ESI) m/z: 223, 193, 180, 167, 151, 137 (100%), 124; HRMS (ESI) for $C_{11}H_{15}N_2OS$ $[M+H]^+$: calcd 223.0905, found 223.0911; Anal. Calcd for $C_{11}H_{14}N_2OS$: C, 59.43; H, 6.35; N, 12.60. Found: C, 59.31; H, 6.25; N, 12.72.

5-Methylthio-2-methyl-4-phenylethynylpyridazin-3(2*H*)-one (6a). This compound was prepared using the general procedure, but instead of dioxane MeOH has been used as the solvent.

No column chromatography was performed. Yield 97%; yellowish solid; mp 131°C (Ethanol); δ_H ($CDCl_3$): 7.67 (s, 1H, H-6), 7.64-7.59 (m, 2H, H_{Ph}-2,6), 7.40-7.32 (m, 3H, H_{Ph}-3,4,5), 3.79 (s, 3H, NCH_3), 2.60 (s, 3H, SCH_3); δ_C ($CDCl_3$): 157.68 (C-3), 147.17 (C-5), 131.26 (C_{Ph}-2,6), 131.79 (C-6), 129.23 (C_{Ph}-4), 128.46 (C-4), 128.28 (C_{Ph}-3,5), 122.32 (C_{Ph}-1), 106.61 (C-2'), 82.10 (C-1'), 40.21 (NCH_3), 14.29 (SCH_3); ν_{max} (KBr): 2924, 2854, 2204, 1641, 1541, 1438, 1229, 1037, 936, 765, 694, 528 cm^{-1}; MS (ESI) m/z: 257 (100%), 242, 214, 200, 186, 129; HRMS (ESI) for $C_{14}H_{13}N_2OS$ $[M+H]^+$: calcd 257.0749, found 257.0748; Anal. Calcd for $C_{14}H_{12}N_2OS$: C, 65.60; H, 4.72; N, 10.93. Found: C, 65.53; H, 4.66; N, 10.85.

5-Methylthio-2-methyl-4-(pent-1-ynyl)pyridazin-3(2*H*)-one (6b). This compound was prepared using the general procedure, but instead of dioxane MeOH has been used as the solvent.

No column chromatography was performed. Yield 38%; Yellowish oil; δ_H ($CDCl_3$): 7.62 (s, 1H, H-6), 3.75 (s, 3H, NCH_3), 2.55 (s, 3H, SCH_3), 2.55 (t, *J* = 7.0 Hz, 2H, H-3′), 1.67 (h, *J* = 7.0 Hz, 2H, H-4′), 1.08 (t, *J* = 7.0 Hz, 3H, H-5′); δ_C ($CDCl_3$): 158.33 (C-3), 146.63 (C-5), 131.43 (C-6), 118.71 (C-4), 109.66 (C-2′), 73.82 (C-1′), 40.30 (NCH_3), 22.35, 21.91 (C-3′ or C-4′), 14.33 (SCH_3), 13.54 (C-5′); ν_{max} (liquid film): 3436, 2962, 2218, 1633, 1546, 1289, 1199, 964 cm^{-1}; MS (ESI) m/z: 223, 179, 153, 134, 116, 98 (100%); HRMS (ESI) for $C_{11}H_{15}N_2OS$ $[M+H]^+$: calcd 223.0905, found 223.0913; Anal. Calcd for $C_{11}H_{14}N_2OS$: C, 59.43; H, 6.35; N, 12.60. Found: C, 59.33; H, 6.24; N, 12.66.

General procedure for the preparation of 2-substituted 6-methylfuro[2,3-*d*]pyridazin-7(6*H*)-ones (7a,b,c) and 2-substituted 5-methylfuro[2,3-*d*]pyridazin-4(5*H*)-ones (9a,b,c):

To a solution of 5-alkynyl-4-chloro- (**1a,b**) or 4-alkynyl-5-chloro-2-methylpyridazin-3(2*H*)-ones (**4a,b**) (1 mmol) in dioxane (9 mL) a KOH solution (0.75 g, 13.4 mmol in 4.6 mL of H_2O) was added. The reaction mixture was stirred at 100°C until total consumption of the starting material (TLC analysis and/or DCI-MS). The reaction mixture was then poured into water (60 mL) and extracted with EtOAc (3x70 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure. The residue was purified by column chromatography.

2-Phenyl-6-methylfuro[2,3-*d*]pyridazin-7(6*H*)-one (7a). Chromatography eluent: Heptane/EtOAc 6:4; Yield 80%; yellowish solid; mp 150.4°C (Ethanol); δ_H ($CDCl_3$): 8.12 (s, 1H, H-4), 7.92-7.88 (m, 2H, H_{Ph}-2,6), 7.51-7.41 (m, 3H, H_{Ph}-3,4,5), 6.91 (s, 1H, H-3), 3.92 (s, 3H, NCH_3); δ_C ($CDCl_3$): 160.20 (C-2), 153.11 (C-7), 146.60 (C-7a), 131.60 (C-4), 129.95 (C_{Ph}-4), 128.89 (C_{Ph}-3,5), 128.49, 128.42 (C_{Ph}-1 or C-3a), 125.49 (C_{Ph}-2,6), 99.54 (C-3), 39.27 (NCH_3); ν_{max} (KBr): 3127, 2924, 2854, 1674, 1541, 1484, 1291, 1012, 920, 767, 689, 652, 492 cm^{-1}; MS (ESI) m/z: 227 (100%), 140; HRMS (ESI) for $C_{13}H_{11}N_2O_2$ $[M+H]^+$: calcd 227.0821, found 227.0813; Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 69.09; H, 4.51; N, 12.29.

2-Propyl-6-methylfuro[2,3-*d*]pyridazin-7(6*H*)-one (7b). Chromatography eluent: Heptane/EtOAc 6:4; Yield 4%; brownish oil; δ_H ($CDCl_3$): 8.04 (s, 1H, H-4), 6.34 (t, *J* = 0.9 Hz, 1H, H-3), 3.89 (s, 3H, NCH_3), 2.79 (td, *J* = 7.5 Hz, 0.9 Hz, 2H, H-1'), 1.79 (h, *J* = 7.5 Hz, 2H, H-2'), 1.00 (t, *J* = 7.5 Hz, 3H, H-3'); δ_C ($CDCl_3$): 164.47 (C-7), 153.32 (C-7a), 146.65, (C-2), 131.77 (C-4), 128.18 (C-3a), 101.14 (C-3), 39.33 (NCH_3), 30.30 (C-1'), 20.97 (C-2'), 13.59 (C-3'); ν_{max} (liquid film): 2960, 2926, 2854, 1681, 1555, 1462, 1288, 1261, 1028, 962, 820, 800 cm^{-1}; MS (ESI) m/z: 193, 164, 139 (100%), 111; HRMS (ESI) for $C_{10}H_{13}N_2O_2$ $[M+H]^+$: calcd 193.0977, found 193.0975; Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.54; H, 6.20; N, 14.67.

2-*t*-Butyl-6-methylfuro[2,3-*d*]pyridazin-7(6*H*)-one (7c). Chromatography eluent: Heptane/Acetone 8:2; Yield 65%; brownish solid; mp 121.1°C (Hexane/Petroleum ether); δ_H ($CDCl_3$): 8.03 (s, 1H, H-4), 6.31 (s, 1H, H-3), 3.89 (s, 3H, NCH_3), 1.40 (s, 9H, *t*-Bu); δ_C ($CDCl_3$): 172.03 (C-2), 153.23 (C-7), 146.48 (C-7a), 131.76 (C-4), 127.92 (C-3a), 98.28 (C-3), 39.22 (NCH_3), 33.38 [$C(\underline{C}H_3)_3$], 28.64 [$\underline{C}(CH_3)_3$]; ν_{max} (KBr): 3123, 2971, 2871, 1670, 1549, 1304, 1040, 931, 655, 466 cm^{-1}; MS (ESI) m/z: 207 (100%), 192, 177, 139, 111; HRMS (ESI) for $C_{11}H_{15}N_2O_2$ $[M+H]^+$: calcd 207.1134, found 207.1129; Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.92; H, 6.76; N, 13.63.

2-Phenyl-5-methylfuro[2,3-*d*]pyridazin-4(5*H*)-one (9a). Chromatography eluent: Heptane/EtOAc 6:4 ; Yield 67%; yellowish solid; mp 178°C (Ethanol); δ_H ($CDCl_3$): 8.21 (d, *J* = 0.6 Hz, 1H, H-7), 7.83-7.79 (m, 2H, H_{Ph}-2,6), 7.50-7.39 (m, 3H, H_{Ph}-3,4,5), 7.25 (d, *J* = 0.6 Hz, 1H, H-3), 3.89 (s, 3H, NCH_3); δ_C ($CDCl_3$): 158.85, 158.45 (C-2 or C-4), 152.45 (C-7a), 129.82, 125.86 (C_{Ph}-4 or C-7), 129.13 (C_{Ph}-3,5), 128.85 (C_{Ph}-1), 125.27 (C_{Ph}-2,6), 124.54 (C-3a), 101.38 (C-3), 39.68 (NCH_3); ν_{max} (KBr): 3117, 2926, 2854, 1668, 1541, 1456, 1376, 1272, 1140, 1011, 954, 911, 820, 772, 760, 694, 655, 496 cm^{-1}; MS (ESI) m/z: 227 (100%), 115; HRMS (ESI) for $C_{13}H_{11}N_2O_2$ $[M+H]^+$: calcd 227.0821, found 227.0824; Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.02; H, 4.46; N, 12.38. Found: C, 68.99; H, 4.40; N, 12.42.

2-Propyl-5-methylfuro[2,3-*d*]pyridazin-4(5*H*)-one (9b). Chromatography eluent: Heptane/Ether 6:4; Yield 3%; dark yellow oil; δ_H ($CDCl_3$): 8.10 (d, *J* = 0.8 Hz, 1H, H-7), 6.66 (q, *J* = 1.0 Hz, 1H, H-3), 3.85 (s, 3H, NCH_3), 2.76 (td, *J* = 7.5, 0.9 Hz, 2H, H-1'), 1.76 (h, *J* = 7.5 Hz, 2H, H-2'), 1.00 (t, *J* = 7.5 Hz, 3H, H-3'); δ_C ($CDCl_3$): 162.25 (C-2), 158.96 (C-4), 152.32 (C-7a), 125.82 (C-7), 123.96 (C-3a), 102.52 (C-3), 39.59 (NCH_3), 30.22 (C-1'), 20.94 (C-2'), 14.09 (C-3'); ν_{max} (liquid film): 2962, 2932, 2874, 1674, 1565, 1463, 1379, 1269, 1125, 1018, 831, 766, 528 cm^{-1}; MS (ESI) m/z: 193, 164 (100%), 139; HRMS (ESI) for $C_{10}H_{13}N_2O_2$ $[M+H]^+$: calcd 193.0977, found 193.0975; Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.32; H, 6.23; N, 14.49.

2-*t*-Butyl-5-methylfuro[2,3-*d*]pyridazin-4(5*H*)-one (9c). Chromatography eluent: Hexane/EtOAc 1:1; Yield 52%; yellowish oil; δ_H ($CDCl_3$): 8.12 (d, *J* = 0.8 Hz, 1H, H-7), 6.65 (d, *J* = 0.8 Hz, 1H, H-3), 3.86 (s, 3H, NCH_3), 1.37 (s, 9H, *t*-Bu); δ_C ($CDCl_3$): 169.99 (C-2), 159.02 (C-4), 152.20 (C-7a), 125.90 (C-7), 123.70 (C-3a), 99.73 (C-3), 39.56 (NCH_3), 33.32 [$\underline{C}(CH_3]$, 28.74 [$C(\underline{C}H_3)]$; ν_{max} (KBr): 3119, 3051, 2970, 2873, 1682, 1558, 1378, 1278, 1143, 1063, 1019, 956, 927, 826, 766, 540 cm^{-1}; MS (ESI) m/z: 207 (100%), 192, 177, 139; HRMS (ESI) for $C_{11}H_{15}N_2O_2$ $[M+H]^+$: calcd 207.1134, found 207.1129; Anal. Calcd for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84; N, 13.58. Found: C, 63.96; H, 6.80; N, 13.49.

General procedure for the preparation of 2-substituted 6-methylthio[2,3-*d*]pyridazin-7(6*H*)-ones (8a,b) and 2-substituted 5-methylthio[2,3-*d*]pyridazin-4(5*H*)-ones (10a,b):

To a solution of 5-alkynyl-4-chloro- (**1a,b**) or 4-alkynyl-5-chloro-2-methylpyridazin-3(2*H*)-ones (**4a,b**) (1 mmol) in DMF (4.6 mL) $Na_2S.9H_2O$ (0.53 g, 2.2 mmol) was added. The reaction mixture was stirred at 60°C until total consumption of the starting material (TLC analysis and/or DCI-MS). The reaction mixture was then poured into water (65 mL) and extracted with CH_2Cl_2 (3x75 mL). After drying over $MgSO_4$, the solvent was removed under reduced pressure. The residue obtained was purified by column chromatography when indicated.

2-Phenyl-6-methylthio[2,3-*d*]pyridazin-7(6*H*)-one (8a). No column chromatography was performed. Yield 72%; light brown solid; mp 191.5°C (Ethanol); δ_H ($CDCl_3$): 8.15 (s, 1H, H-4), 7.71-7.66 (m, 2H, H_{Ph}-2,6), 7.49-7.39 (m, 4H, H-3 and H_{Ph}-3,4,5), 3.88 (s, 3H, NCH_3); δ_C ($CDCl_3$): 157.27, 153.34 (C-7 or C-7a), 140.17 (C-3a), 135.98 (C-2), 132.74 (C_{Ph}-1), 132.72 (C-4), 129.67 (C_{Ph}-4), 129.32 (C_{Ph}-3,5), 126.80 (C_{Ph}-2,6), 118.26 (C-3), 39.32 (NCH_3); ν_{max} (KBr): 3088, 3058, 1636, 1468, 1349, 1242, 1021, 852, 753, 682, 455 cm^{-1}; MS (ESI) m/z: 243 (100%), 186, 115; HRMS (ESI) for $C_{13}H_{11}N_2OS$ $[M+H]^+$: calcd 243.0592, found 243.0585; Anal. Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.47; H, 4.10; N, 11.66.

2-Propyl-6-methylthio[2,3-*d*]pyridazin-7(6*H*)-one (8b). Chromatography eluent: Heptane/EtOAc 6:4; Yield 60%; light yellow solid; mp 67.5°C (Hexane/Petroleum ether); δ_H ($CDCl_3$): 8.07 (s, 1H, H-4), 7.00 (t, *J* = 1.1 Hz, 1H, H-3), 3.86 (s, 3H, NCH_3), 2.91 (td, *J* = 7.5, 1.1 Hz, 2H, H-1'), 1.79 (h, *J*= 7.5 Hz, 2H, H-2'), 1.01 (t, *J* = 7.3 Hz, 3H, H-3'); δ_C ($CDCl_3$): 157.36, 155.96 (C-7 or C-7a), 139.72 (C-3a), 135.57 (C-2), 132.54 (C-4), 120.03 (C-3), 39.24 (NCH_3), 32.75 (C-1'), 24.52 (C-2'), 13.54 (C-3'); ν_{max} (KBr): 3093, 2959, 2870, 1629, 1567, 1464, 1345, 1224, 1024, 878, 669, 445 cm^{-1}; MS (ESI) m/z: 209, 180 (100%); HRMS (ESI) for $C_{10}H_{13}N_2OS$ $[M+H]^+$: calcd 209.0749, found 209.0742; Anal. Calcd for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.81; N, 13.45. Found: C, 57.60; H, 5.83; N, 13.39.

2-Phenyl-5-methylthio[2,3-*d*]pyridazin-4(5*H*)-one (10a). No column chromatography was performed. Yield 79%; brownish solid; mp 212°C (decomp, Ethanol); δ_H ($CDCl_3$): 8.17 (d, *J* = 0.8 Hz, 1H, H-7), 7.89 (d, *J* = 0.8 Hz, 1H, H-3), 7.70-7.66 (m, 2H, H_{Ph}-2,6), 7.47-7.37 (m, 3H, H_{Ph}-3,4,5), 3.87 (s, 3H, NCH_3); δ_C ($CDCl_3$): 157.66 (C-4), 149.86 (C-7a), 138.82 (C-3a), 137.14 (C-2), 132.69 (C_{Ph}-1), 131.37 (C-7), 129.48 (C_{Ph}-4), 129,31 (C_{Ph}-3,5), 126.65 (C_{Ph}-2,6), 119.88 (C-3), 39.40 (NCH_3); ν_{max} (KBr): 3075, 2925, 1651, 1467, 1240, 1049, 954, 881, 758, 689, 627, 525 cm^{-1}; MS (ESI) m/z: 243 (100%), 186, 115; HRMS (ESI) for $C_{13}H_{11}N_2OS$ $[M+H]^+$: calcd 243.0592, found 243.0593; Anal. Calcd for $C_{13}H_{10}N_2OS$: C, 64.44; H, 4.16; N, 11.56. Found: C, 64.39; H, 4.08; N, 11.50.

2-Propyl-5-methylthio[2,3-*d*]pyridazin-4(5*H*)-one (10b). Chromatography eluent: Heptane/Ether 1:1; Yield 19%; dark yellow oil; δ_H ($CDCl_3$): 8.11 (d, *J* = 0.6 Hz, 1H, H-7), 7.41 (q, *J* = 0.8 Hz, 1H, H-3), 3.85 (s, 3H, NCH_3), 2.90 (td, *J* = 7.5, 1.0 Hz, 2H, H-1'), 1.78 (h, *J* = 7.3 Hz, 2H, H-2'), 1.01 (t, *J* = 7.3 Hz, H-3'); δ_C ($CDCl_3$): 157.65 (C-4), 152.37 (C-7a), 138.62 (C-3a), 136.52 (C-2), 131.46 (C-7), 121.50 (C-3), 39.31 (NCH_3), 32.49 (C-1'), 24.48 (C-2'), 13.52 (C-3'); ν_{max} (liquid film): 3094, 3032, 2962, 2931, 2901, 2870, 1637, 1481, 1042, 954, 843, 766, 631, 497 cm^{-1}; MS (ESI) m/z: 209, 180 (100%), 167;

HRMS (ESI) for $C_{10}H_{13}N_2OS$ $[M+H]^+$: calcd 209.0749, found 209.0753; Anal. Calcd for $C_{10}H_{12}N_2OS$: C, 57.67; H, 5.81; N, 13.45. Found: C, 57.59; H, 5.70; N, 13.32.

Preparation of 5-*t*-Butylethynyl-4-chloro-2-methyl- (7c) and 4-*t*-Butylethynyl-5-chloro-2-methyl-pyridazin-3(2*H*)-one (9c):

The procedure for the preparation of these compounds is described in a previous publication.[1]

5-*t*-Butylethynyl-4-chloro-2-methylpyridazin-3(2*H*)-one (7c). Chromatography eluent: Heptane/ EtOAc 8:2; Yield 30%; brown oil; δ_H ($CDCl_3$): 7.62 (s, 1H, H-6), 3.80 (s, 3H, NCH_3), 1.35 (s, 9H, *t*-Bu); δ_C ($CDCl_3$): 157.16 (C-3), 136.59 (C-6), 130.21 (C-4), 126.72 (C-5), 114.00 (C-2'), 72.15 (C-1'), 40.88 (NCH_3), 30.43 [$C(\underline{C}H_3)_3$], 28.74 [$\underline{C}(CH_3)_3$]; ν_{max} (liquid film): 2972, 2871, 2360, 2229, 1657, 1587, 1367, 1286, 1241, 864, 676 cm^{-1}; MS (ESI) m/z: 225 (100%), 210, 132; HRMS (ESI) for $C_{11}H_{14}N_2OCl$ $[M+H]^+$: calcd 225.0795, found 225.0802; Anal. Calcd for $C_{11}H_{13}N_2ClO$: C, 58.80; H, 5.83; N, 12.47. Found: C, 58.84; H, 5.93; N, 12.37.

4-*t*-Butylethynyl-5-chloor-2-methylpyridazin-3(2*H*)-one (9c). Chromatography eluent: Heptane/EtOAc 8:2; Yield 30%; light yellow solid; mp 94.2°C (Hexane/Ether); δ_H ($CDCl_3$): 7.72 (s, 1H, H-6), 3.75 (s, 3H, NCH_3), 1.37 (s, 9H, *t*-Bu); δ_C ($CDCl_3$): 158.90 (C-3), 139.20 (C-5), 135.86 (C-6), 124.00 (C-4), 116.99 (C-2'), 71.48 (C-1'), 40.45 (NCH_3), 30.53 [$C(\underline{C}H_3)_3$], 28.97 [$\underline{C}(CH_3)_3$]; ν_{max} (KBr): 3085, 3055, 2972, 2930, 2214, 1644, 1564, 1456, 1288, 1246, 1036, 947, 852, 630 cm^{-1}; MS (ESI) m/z: 225, 189, 183, 157, 127 (100%); HRMS (ESI) for $C_{11}H_{14}N_2OCl$ $[M+H]^+$: calcd 225.0795, found 225.0785; Anal. Calcd for $C_{11}H_{13}N_2ClO$: C, 58.80; H, 5.83; N, 12.47. Found: C, 58.67; H, 5.80; N, 12.45.

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2. For transformations of the triple bond to several other functional groups see: Richard Larock 'Comprehensive Organic Transformations: A Guide to Functional Group Transformations' foreword by H. C. Brown, VCH Publishers, Inc. New York, 1989.

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5. After work-up of the reaction mixtures (see EXPERIMENTAL Part: General procedures) ^{1}H-NMR and DCI-MS spectra revealed the presence of several reaction products which could not be separated: **4a** + $NaSCH_3$/dioxane: 5-chloro-2-methyl-4-[(*E* and *Z*)-2-methylsulfanyl-2-phenylvinyl]pyridazin-3(2*H*)-one.

   4b + $NaOCH_3$/dioxane: 5-chloro-4-[(1*E* and 1*Z*)-2-methoxypent-1-enyl]-2-methylpyridazin-3(2*H*)-one and unidentified compound.

   4b + $NaSCH_3$/dioxane: 5-chloro-2-methyl-4-[(1*E* and 1*Z*)-2-methylsulfanylpent-1-enyl]pyridazin-3(2H)-one.
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