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THERMOLYSIS OF 5-AZIDO-4-ARYLPYRIDAZIN-3(2*H*)-ONES: AN EFFICIENT AND VERSATILE SYNTHESIS OF PYRIDAZINO[4,5-*b*]INDOLES

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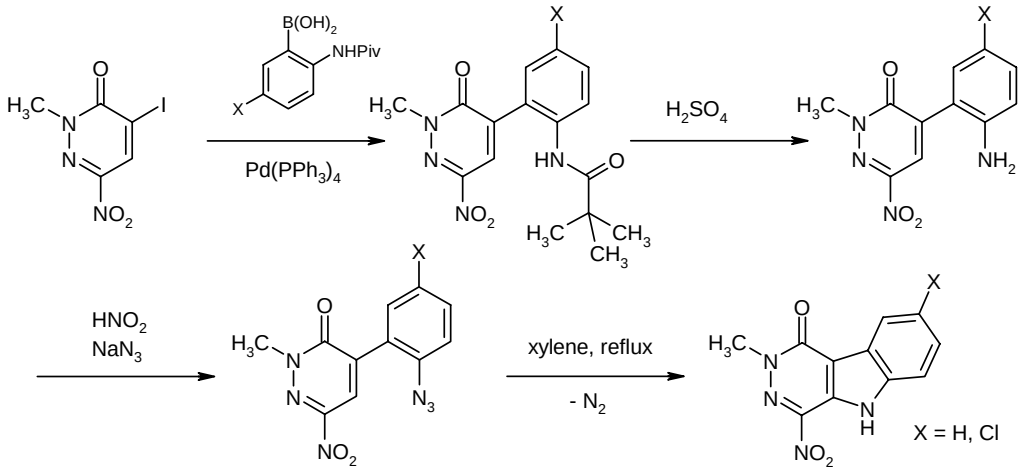
Abstract – 5-Azido-4-arylpyridazin-3(2*H*)-ones, which are easily available from 4,5-dihalopyridazin-3(2*H*)-ones in few steps, were found to undergo in high yields a thermally induced cyclization into pyridazino[4,5-*b*]indole derivatives ("aza-carbolinones") by formation of the N-5/C-5a bond *via* a nitrene insertion process. This new method is complementary to a previously reported pathway in which the C-4a/N-5 bond of the ring system is formed.

INTRODUCTION

The pyridazino[4,5-*b*]indole ring system, which has been known for several decades, constitutes the core structure of a large variety of bio-active compounds, such as antihypertensive,[1] antiarrhythmic,[2] positive inotropic,[3] thromboxane A_2 synthetase inhibitory,[4] MAO inhibitory,[5] serotonine antagonistic,[6] anti-histaminic,[7] anxiolytic,[8] or HIV-1 reverse transcriptase inhibitory[9] agents. This broad spectrum of biological/pharmacological activities is not surprising in view of the close structural similarity ("bio-isosterism") of the title ring system with β-carboline as well as γ-carboline which both, in turn, represent the backbone of numerous biologically active compounds. Many of these "aza-carbolines" of the pyridazino[4,5-*b*]indole type feature at least one heteroelement substituent at the pyridazine ring, and they are typically prepared by condensation of appropriately 2,3-disubstituted indoles such as dicarboxylic acid derivatives or *ortho*-keto carboxylic acid derivatives with hydrazine.[10] Among the alternative strategies for the construction of this ring system, the sequence recently reported by Riedl *et al.*[11] for the preparation of

* *Dedicated with best wishes to Professor Miha Tišler on the occasion of his 80th birthday*

2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-ones deserves particular attention. Here, the benzene and the pyridazine units are first connected by a Suzuki coupling of a halopyridazine with an arylboronic acid, then the central pyrrole ring is formed by thermolysis of an azido intermediate which is obtained in several steps from a pivaloylamino precursor (see Scheme 1). A similar approach had been used previously for the synthesis of isomeric 3,5-dihydro-4*H*-pyridazino[4,5-*b*]indol- 4-ones.[12,13] In all of these cases, the azido group is placed at the benzene unit so that the thermally generated nitrene attacks the pyridazine ring. Consequently, aryl boronic acids with a suitable functionality in *ortho* position must be employed in the Suzuki coupling, in order to generate the requisite azide later on. Such building blocks, in turn, can be prepared *via ortho*-lithiated pivalanilides.[14]



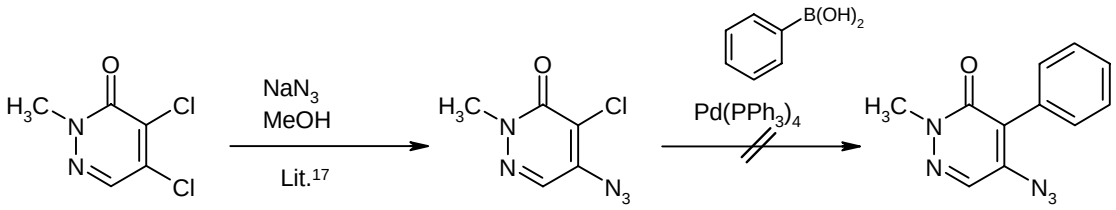
Scheme 1. Synthesis of 2,5-dihydro-4-nitro-1*H*-pyridazino[4,5-*b*]indol-1-ones[11]

As we needed an efficient and highly flexible access to new representatives of this ring system in the course of an ongoing study, we considered it worthwhile to develop an alternative synthetic pathway which would be complementary to the route shown in Scheme 1. By placing the azido group at the pyridazinone unit, it should be possible to use simple, commercially available arylboronic acids in the first step. Here, we wish to report on the implementation of this strategy by the preparation of selected derivatives of the target structure.

RESULTS AND DISCUSSION

In principle, either the aryl residue or the azido group can be first attached to the pyridazinone scaffold, if a suitable precursor is available. As it is known that N-protected 4,5-dichloropyridazin-3(2*H*)-ones cannot be regioselectively monoarylated at position 4 under Suzuki conditions,[15,16] we first investigated the possibility of arylating a halopyridazinone which bears already an azido functionality. Thus, in an exploratory experiment we reacted 5-azido-4-chloro-2-methylpyridazin-3(2*H*)-one[17] (which is easily

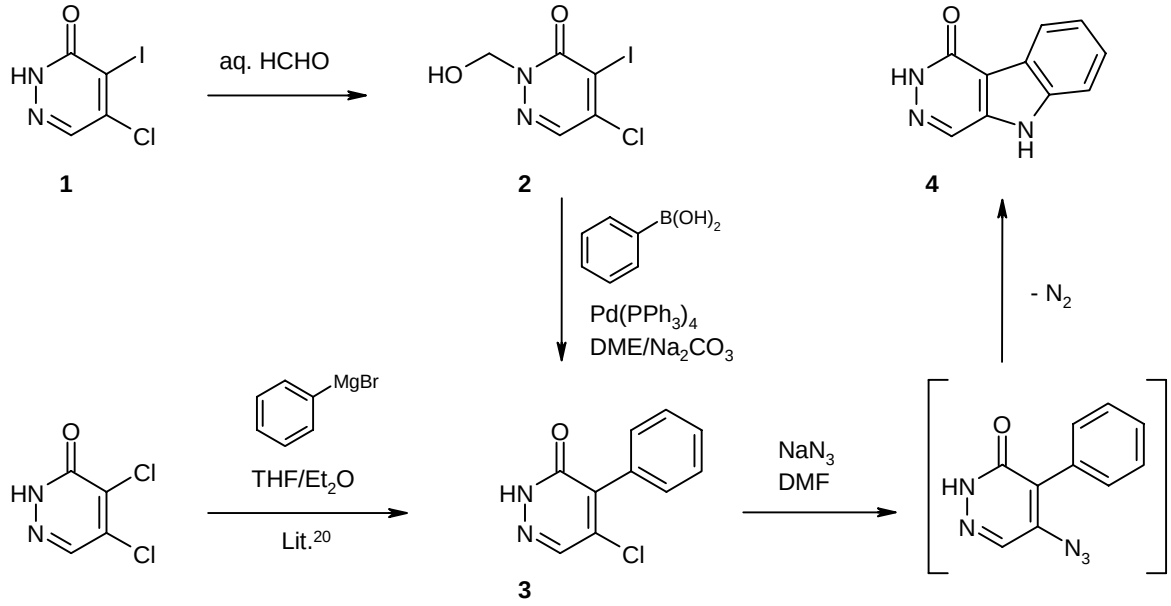
available from 4,5-dichloro-2-methylpyridazin-3(2*H*)-one by treatment with sodium azide in methanol) with benzeneboronic acid in the presence of tetrakis(triphenylphosphine)palladium(0) in a mixture of toluene and aqueous sodium carbonate under standard Suzuki conditions. It turned out, however, that the presence of an azido group is incompatible with this method, as the reaction mixture turned black very quickly and work-up of the mixture mainly gave unreacted starting material. It can be assumed that under the conditions employed, a Staudinger-type reaction between the azide and the triphenylphosphine of the catalyst takes place, thus immediately depriving the palladium of its ligand.



Scheme 2.

Therefore, we decided to introduce the azido function after the Suzuki arylation of the starting material. Taking advantage of the superior reactivity of iodine compared to chlorine in such palladium-catalyzed cross-coupling reactions, which had been recently demonstrated for a similar substrate by Stevenson *et al.*,[18] we succeeded in the selective 4-arylation of 4-iodo-5-chloropyridazin-3(2*H*)-one (**1**) *via* the *N*-substituted derivative (**2**) (using the labile hydroxymethyl protecting group as proposed by Sotelo *et al.*[19]). Whereas this approach should be also applicable to a variety of other arylboronic acids and thus offers some flexibility regarding the aryl substituent, yields are only moderate (approx. 40%) and they could not be improved without losing selectivity with respect to monoarylation. On the other hand, 5-chloro-4-phenylpyridazin-3(2*H*)-one (**3**) can be also prepared very conveniently from commercially available 4,5-dichloropyridazin-3(2*H*)-one by treatment with excess phenylmagnesium bromide in THF/diethyl ether at room temperature, as described in a patent.[20] In the phenyl compound (**3**), the chloro function at position 5 of the diazine was expected to be sufficiently reactive towards nucleophilic displacement by an azido group. Indeed, when **3** was heated with sodium azide in dimethylformamide at 120°C, a slow reaction was observed, being complete after 17 hours. The product obtained in 70% yield was not the 5-azido compound, but the tricyclic pyridazinone (**4**), which was identified by comparison of its spectral data (^{1}H-NMR, IR) with those reported in the literature.[21] Obviously, under these reaction

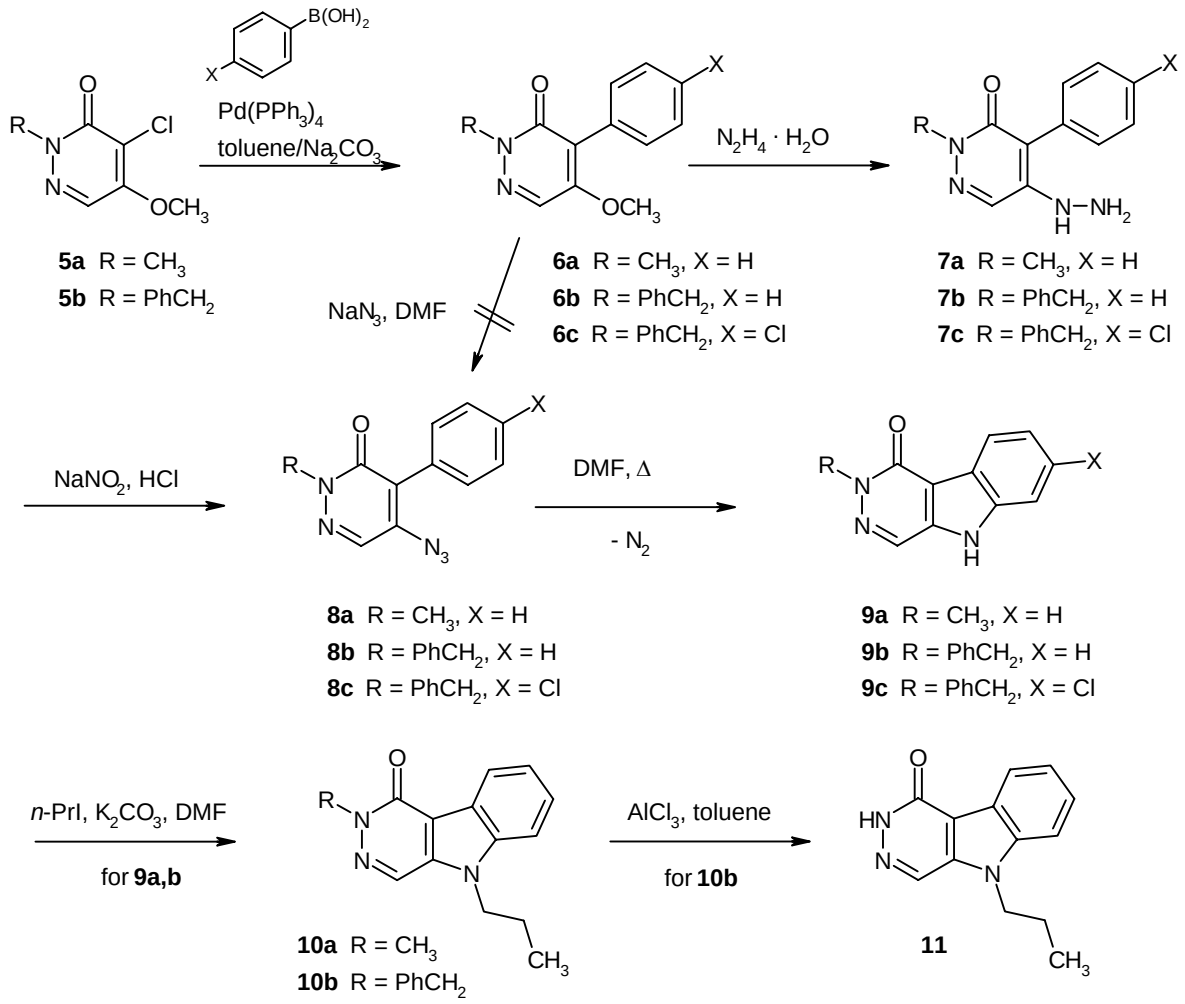
conditions not only the nucleophilic substitution takes place, but also thermal degradation of the intermediate azide, followed by nitrene insertion into the *ortho* C–H bond of the phenyl moiety, thus affording the target tricycle in a simple and convenient one-pot reaction (Scheme 3).



Scheme 3.

In search for a more flexible approach, we investigated 2-alkyl-4-chloro-5-methoxypyridazin-3(2*H*)-ones as an alternative type of *N*-substituted starting material, and these compounds actually turned out to be an excellent choice. As it had been demonstrated by Mátyus et al.,[22] alkoxy derivatives of this type are well-suited for selectively and temporarily blocking position 5 of the initial educt, 4,5-dichloro-pyridazin-3(2*H*)-one, and they are very easily available in one step from the latter. Thus, compounds (**6a,b**) were prepared in high yield according to lit.[15,23] under standard Suzuki conditions, and the new 4-chlorophenyl derivative (**6c**) was obtained analogously in excellent yield.

Initial attempts to directly replace the methoxy substituent in compounds (**6**) by an azido group by heating with sodium azide in dimethylformamide were unsuccessful. However, the requisite azido functionality can be smoothly introduced by a two-step procedure *via* the corresponding 5-hydrazino compounds (**7a-c**) (Scheme 4). These intermediates were obtained in good yields by refluxing the ethers (**6a-c**) in hydrazine hydrate for 2 hours, and they could be easily converted into the azides (**8a-c**) by treatment with nitrous acid at 0°C (Scheme 4).



Scheme 4.

The azido compound (**8a**), when heated to 130°C in an inert solvent (dimethylformamide) underwent the desired thermolysis and subsequent nitrene insertion reaction very smoothly, affording the known 2,5-dihydro-2-methyl-1*H*-pyridazino[4,5-*b*]indol-1-one[21,24] (**9a**) in 80% yield. Under the same conditions, cyclization of the *N*-benzylpyridazinones (**8b,c**) gave the hitherto unknown pyridazino[4,5-*b*]indoles (**9b,c**) almost quantitatively. It should be noted that this thermolysis is a very clean reaction. When it was carried out in an NMR tube (DMSO-d_6 as solvent), not even traces of signals other than those of the educt and the product were detectable in the ^{1}H-NMR spectrum in the course of the transformation.

In addition to the N-2-substituted 2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-ones of type **9**, other representatives of this ring system with a variable N-substitution pattern are easily available. As position 2 is already blocked, treatment of such compounds with alkylating agents gives 2,5-disubstituted derivatives

in good yields, as exemplified by the synthesis of the 2,5-dialkyl compounds (**10a,b**). Moreover, if the substituent at N-2 is a benzyl group, an easy access to 5-monosubstituted products is provided by *N*-debenzylation with aluminium trichloride in toluene,[25] as demonstrated by transformation of **10b** into **11**.

In conclusion, it can be stated that thermolysis of 5-azido-4-arylpyridazin-3(2*H*)-ones offers a very useful method for the synthesis of aza-carbolinones of the 2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one type with inherent variability with regard to their substitution pattern, especially at the nitrogen atoms N-2 and N-5. Moreover, the *N*-unsubstituted parent compound can be conveniently prepared by this method in only two steps from a commercially available starting material.

EXPERIMENTAL

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 (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on a Varian Unity*plus* 300 spectrometer (δ values in ppm). MS spectra were obtained with a Hewlett-Packard 5890A/5970B GC/MS spectrometer or with a Shimadzu QP5050A spectrometer. HRMS spectra were taken on a Finnigan MAT 8230 instrument at the Institute of Organic Chemistry, University of Vienna. Column chromatography was done on Merck Kieselgel 60, 0.063-0.200 mm. Light petroleum refers to the fraction of bp 50–70°C. Elemental analyses were performed at the Microanalytical Laboratory, Faculty of Chemistry, University of Vienna.

5-Chloro-4-iodopyridazin-3(2*H*)-one (1).

To a solution of 4-chloro-5-hydroxy-3-iodofuran-2(5*H*)-one[26] (6.51 g, 25 mmol) in EtOH (50 mL) was added dropwise a solution of 100% hydrazine hydrate (1.35 g, 27 mmol) in EtOH (5 mL). The mixture was refluxed for 4 h, then it was chilled and stored in the refrigerator overnight. The precipitate was collected by filtration, washed with EtOH and dried to afford **1** (5.78 g; 90%) as pale yellow crystals, mp 207–208°C (EtOH). *Anal.* Calcd for $C_4H_2ClIN_2O$: C, 18.74; H, 0.79; N, 10.92. Found: C, 19.00; H, 0.96; N, 11.11. MS: m/z (rel. int.) 258 (M^+, 36%), 256 (M^+, 100), 206 (27), 205 (36), 199 (16), 149 (14), 129 (32), 127 (15), 81 (16), 73 (21), 69 (28). IR (cm^{-1}): 3262, 3215, 3166, 3111, 3017, 2989, 2934, 2863, 1641, 1578, 1520, 1165, 1130, 1039, 928, 866, 732, 597, 551. ^{1}H-NMR (DMSO-d_6) δ: 13.31 (s, 1H, NH), 7.83 (s, 1H, 6-H). ^{13}C-NMR (DMSO-d_6) δ: 159.4, 144.7, 135.3, 111.3.

5-Chloro-2-hydroxymethyl-4-iodopyridazin-3(2*H*)-one (2).

A suspension of **1** (1026 mg, 4 mmol) in 36% aqueous formaldehyde (15.3 mL, 200 mmol) was refluxed under argon for 1 h. The clear solution was chilled and kept in the refrigerator for 24 h. The precipitate was

collected by filtration, washed with water, and dried to give **2** (900 mg; 79%) as colorless crystals, mp 214–216°C (water). *Anal.* Calcd for $C_5H_4N_2O_2ClI$: C, 20.96; H, 1.41; N, 9.78. Found: C, 20.88; H, 1.34; N, 10.03. IR (cm^{-1}): 3381, 3074, 2967, 1639, 1561, 1406, 1195, 1160, 1085, 946, 751, 711, 640. ^{1}H-NMR (DMSO-d_6) δ: 7.94 (s, 1H, 6-H), 6.89 (t, J = 7.7 Hz, 1H, OH), 5.34 (d, J = 7.7 Hz, 2H, CH_2). ^{13}C-NMR (DMSO-d_6) δ: 157.9, 144.5, 135.0, 111.4, 74.8.

5-Chloro-4-phenylpyridazin-3(2*H*)-one (3).[20]

A mixture of **2** (430 mg, 1.5 mmol) and $Pd(PPh_3)_4$ (45 mg, 0.039 mmol) in DME (15 mL) was flushed with argon for 15 min. A solution of Na_2CO_3 (318 mg, 3 mmol) in water (5 mL) was added, followed by benzeneboronic acid (183 mg, 1.5 mmol). The mixture was stirred and refluxed under argon for 48 h, then it was evaporated to dryness under reduced pressure. EtOAc (30 mL) was added, and the flask was placed in an ultrasonic bath for 30 min. The suspension was filtered through Celite and the filtrate was concentrated and subjected to column chromatography (eluent: CH_2Cl_2/EtOAc, 9+1). Evaporation of the eluate gave **3** (127 mg, 41%) as pale yellow crystals, mp 183–184°C (EtOAc; lit.[20]: 193–195°C). *Anal.* Calcd for $C_{10}H_7N_2OCl$: C, 58.13; H, 3.41; N, 13.56. Found: C, 57.97; H, 3.60; N, 13.39. MS: m/z (rel. int.) 208 (M^+, 26%), 207 (69), 206 (M^+, 65), 205 (100), 149 (60), 115 (34), 114 (39). IR (cm^{-1}): 3429, 3420, 3126, 3014, 2965, 2887, 1645, 1491, 1443, 1161, 1012, 879, 698, 593. ^{1}H-NMR (DMSO-d_6) δ: 13.42 (s, 1H, NH), 8.08 (s, 1H, 6-H), 7.50–7.39 (m, 5H, phenyl-H). ^{13}C-NMR (DMSO-d_6) δ: 159.6, 137.8, 137.5, 135.6, 131.0, 129.5, 129.4, 129.0, 128.0, 127.9.

2,5-Dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (4).[21]

A mixture of **3** (206 mg, 1 mmol) and NaN_3 (130 mg, 2 mmol) in DMF (15 mL) was stirred at 120°C for 17 h. It was then evaporated to dryness under reduced pressure, the residue was washed with water (20 mL) and dried to give **4** (130 mg; 70%) as yellow crystals, mp >320°C (water; lit.[21]: >320°C). MS: m/z (rel. int.) 186 (17%), 185 (M^+, 100), 129 (27), 128 (26), 102 (25), 101 (24), 75 (9), 51 (11). IR (cm^{-1}): 3206, 2954, 2924, 1647, 1624, 1573, 1450, 1424, 1398, 1330, 1268, 1244, 1129, 1086, 876, 821, 779, 725, 690, 594. ^{1}H-NMR (DMSO-d_6) δ: 12.63 (s, 1H, NH), 12.50–11.80 (br s, 1H, NH), 8.37 (s, 1H, 4-H), 8.18–8.13 (m, 1H, 9-H), 7.68–7.63 (m, 1H, 6-H), 7.51–7.40 (m, 1H, 7-H), 7.34–7.28 (m, 1H, 8-H). ^{13}C-NMR (DMSO-d_6) δ: 159.9, 138.4, 137.3, 128.1, 126.5, 122.5, 122.0, 121.9, 113.0, 111.9.

2-Benzyl-4-(4-chlorophenyl)-5-methoxypyridazin-3(2*H*)-one (6c).

A mixture of 2-benzyl-4-chloro-5-methoxypyridazin-3(2*H*)-one[23] (**5b**) (1003 mg, 4 mmol) and 4-chloro-benzeneboronic acid (938 mg, 6 mmol) in toluene (24 mL) was flushed with argon for 5 min, followed by addition of $Pd(PPh_3)_4$ (140 mg, 0.12 mmol) and 2M aqueous Na_2CO_3 (4.4 mL). The mixture was stirred and

refluxed under argon for 16 h, then it was evaporated to dryness under reduced pressure. EtOAc (50 mL) was added, and the flask was placed in an ultrasonic bath for 20 min. The suspension was filtered through Celite and the filtrate was concentrated and subjected to column chromatography (eluent: light petroleum/EtOAc, 3+1). Evaporation of the eluate gave **6c** (1240 mg, 95%) as a colorless oil which slowly crystallized in the refrigerator, mp 94–96°C (light petroleum). *Anal.* Calcd for $C_{18}H_{15}N_2O_2Cl$: C, 66.16; H, 4.63; N, 8.57. Found: C, 66.41; H, 4.52; N, 8.38. MS: m/z (rel. int.) 328 (M^+, 36%), 326 (M^+, 100), 297 (7), 295 (18), 224 (20), 222 (57), 181 (20), 179 (60), 138 (14), 136 (35), 106 (25), 91 (88), 65 (25). IR (cm^{-1}): 3034, 2954, 1631, 1590, 1491, 1398, 1348, 1334, 1264, 1159, 1018, 972, 824, 737, 711, 695. ^{1}H-NMR ($CDCl_3$) δ: 7.92 (s, 1H, 6-H), 7.50–7.45 (m, 4H, phenyl-H), 7.40–7.29 (m, 5H, phenyl-H), 5.37 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3). ^{13}C-NMR ($CDCl_3$) δ: 160.6, 154.6, 136.3, 134.1, 131.8, 128.9, 128.6, 128.5, 128.0, 127.9, 127.6, 120.2, 57.1, 55.6.

5-Hydrazino-2-methyl-4-phenylpyridazin-3(2*H*)-one (7a).

A mixture of 5-methoxy-2-methyl-4-phenylpyridazin-3(2*H*)-one[15] (**6a**) (432 mg, 2 mmol) and 100% hydrazine hydrate (15 mL) was refluxed under argon for 2 h. It was then evaporated to dryness under reduced pressure, the residue was washed with water and dried to give **7a** (324 mg; 75%) as colorless crystals, mp 218–219°C (water). *Anal.* Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.59; N, 25.91. Found: C, 61.37; H, 5.58; N, 25.63. MS: m/z (rel. int.) 216 (M^+, 100%), 215 (88), 145 (18), 128 (22), 115 (23), 102 (25), 89 (17), 77 (16). IR (cm^{-1}): 3446, 3301, 3252, 1641, 1605, 1585, 1539, 1491, 1449, 1404, 1356, 1298, 1242, 1101, 1041, 886, 773, 756, 701, 611. ^{1}H-NMR (DMSO-d_6) δ: 8.20 (s, 1H, 6-H), 7.44–7.38 (m, 2H, phenyl-H), 7.35–7.23 (m, 3H, phenyl-H), 6.82 (s, 1H, NH), 4.27 (s, 2H, NH_2), 3.55 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 159.0, 146.8, 132.2, 130.1, 128.3, 128.2, 127.3, 108.0, 39.1.

2-Benzyl-5-hydrazino-4-phenylpyridazin-3(2*H*)-one (7b).

A mixture of 2-benzyl-5-methoxy-4-phenylpyridazin-3(2*H*)-one[23] (**6b**) (584 mg, 2 mmol) and 100% hydrazine hydrate (15 mL) was refluxed under argon for 2 h. It was then evaporated to dryness under reduced pressure, the residue was washed with water and dried to give **7b** (485 mg; 83%) as colorless crystals, mp 117–118°C (water). HRMS Calcd for $C_{17}H_{16}N_4O$: 292.1324. Found: 292.1322. MS: m/z (rel. int.) 292 (M^+, 50%), 186 (40), 106 (92), 102 (38), 91 (100), 77 (36), 65 (35), 57 (27). IR (cm^{-1}): 3510, 3464, 3213, 1635, 1603, 1569, 1495, 1420, 1329, 1312, 1040, 778, 753, 705. ^{1}H-NMR (DMSO-d_6) δ: 8.26 (s, 1H, 6-H), 7.43–7.38 (m, 2H, phenyl-H), 7.35–7.25 (m, 8H, phenyl-H), 6.94 (s, 1H, NH), 5.17 (s, 2H, CH_2), 4.30 (s, 2H, NH_2). ^{13}C-NMR (DMSO-d_6) δ: 158.8, 146.7, 137.8, 132.2, 130.1, 128.8, 128.3, 127.7, 127.3, 108.0, 53.5.

2-Benzyl-4-(4-chlorophenyl)-5-hydrazinopyridazin-3(2*H*)-one (7c).

A mixture of **6c** (653 mg, 2 mmol) and 100% hydrazine hydrate (15 mL) was refluxed under argon for 2 h. It was then evaporated to dryness under reduced pressure and the residue was recrystallized from EtOH/water to give **7c** (530 mg; 81%) as colorless crystals, mp 168–171°C. HRMS Calcd for $C_{17}H_{15}ClN_4O$: 326.0934. Found: 326.0944. MS: m/z (rel. int.) 328 (M^+, 18%), 326 (M^+, 55), 222 (11), 221 (13), 220 (20), 186 (12), 179 (12), 164 (12), 136 (13), 106 (100), 91 (76), 65 (16). IR (cm^{-1}): 3521, 3466, 3212, 3067, 1633, 1602, 1574, 1561, 1491, 1427, 1395, 1096, 1030, 828, 755, 703. ^{1}H-NMR (DMSO-d_6) δ: 8.26 (s, 1H, 6-H), 7.46–7.42 (BB' part of an AA'BB' system, 2H, phenyl-H), 7.32–7.24 (m, 7H, phenyl-H), 7.21 (br s, 1H, NH), 5.16 (s, 2H, CH_2), 4.31 (br s, 2H, NH_2). ^{13}C-NMR (DMSO-d_6) δ: 158.6, 146.9, 137.8, 132.2, 131.8, 131.2, 128.8, 128.3, 127.7, 127.2, 106.5, 53.5.

5-Azido-2-methyl-4-phenylpyridazin-3(2*H*)-one (8a).

To an ice-cooled suspension of **7a** (216 mg, 1 mmol) in conc HCl (5 mL) was added dropwise a solution of $NaNO_2$ (345 mg, 5 mmol) in water (5 mL). The cooling bath was removed and the mixture was stirred for 10 min. It was then diluted with water (20 mL) and extracted with Et_2O (3 × 30 mL). The combined extracts were washed with aqueous $NaHCO_3$ and water and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford **8a** (181 mg; 80%) as yellow crystals, mp 108–109°C (Et_2O). *Anal.* Calcd for $C_{11}H_9N_5O$: C, 58.15; H, 3.99; N, 30.82. Found: C, 58.21; H, 3.86; N, 30.12. MS: m/z (rel. int.) 227 (M^+, 17%), 199 (29), 171 (19), 156 (12), 143 (36), 128 (100), 115 (82), 101 (33), 89 (31), 77 (30), 56 (39), 51 (31). IR (cm^{-1}): 3446, 2118, 1631, 1590, 1495, 1445, 1388, 1291, 863, 787, 698, 655, 619, 545. ^{1}H-NMR (DMSO-d_6) δ: 8.11 (s, 1H, 6-H), 7.42–7.38 (m, 5H, phenyl-H), 3.67 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 158.9, 138.8, 131.1, 130.4, 130.0, 128.5, 127.6, 124.9, 40.0.

5-Azido-2-benzyl-4-phenylpyridazin-3(2*H*)-one (8b).

To an ice-cooled suspension of **7b** (292 mg, 1 mmol) in conc HCl (5 mL) was added dropwise a solution of $NaNO_2$ (345 mg, 5 mmol) in water (5 mL). The cooling bath was removed and the mixture was stirred for 10 min. It was then diluted with water (20 mL) and extracted with Et_2O (3 × 30 mL). The combined extracts were washed with aqueous $NaHCO_3$ and water and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to afford **8b** (242 mg; 80%) as yellow crystals, mp 88°C (Et_2O). *Anal.* Calcd for $C_{17}H_{13}N_5O$: C, 67.32; H, 4.32; N, 23.09. Found: C, 67.56; H, 4.26; N, 22.81. MS: m/z (rel. int.) 303 (M^+, 1%), 275 (5), 258 (4), 246 (3), 231 (5), 219 (2), 171 (13), 143 (25), 128 (22), 115 (15), 106 (31), 91 (100), 77 (22), 65 (24). IR (cm^{-1}): 3423, 3059, 2958, 2299, 2216, 2112, 1637, 1593, 1491, 1452, 1425, 1403, 1348, 1330, 1292, 1255, 1216, 1069, 1000, 869, 780, 750, 722, 701, 651, 561. ^{1}H-NMR (DMSO-d_6) δ: 8.17 (s, 1H,

6-H), 7.44–7.38 (m, 5H, phenyl-H), 7.35–7.30 (m, 5H, phenyl-H), 5.27 (s, 2H, CH_2). ^{13}C-NMR (DMSO-d_6) δ: 158.7, 138.9, 136.7, 131.9, 130.4, 130.1, 128.6, 128.4, 128.0, 127.6, 127.5, 125.2, 54.5.

5-Azido-2-benzyl-4-(4-chlorophenyl)pyridazin-3(2*H*)-one (8c).

To an ice-cooled suspension of **7c** (326 mg, 1 mmol) in conc HCl (5 mL) was added dropwise a solution of $NaNO_2$ (345 mg, 5 mmol) in water (5 mL). The cooling bath was removed and the mixture was stirred for 10 min. It was then diluted with water (20 mL) and extracted with Et_2O (3 × 30 mL). The combined extracts were washed with aqueous $NaHCO_3$ and water and dried over Na_2SO_4. The solvent was evaporated at rt under reduced pressure to afford **8c** (300 mg, 89%) as a thermolabile, pale yellow oil which was used for the subsequent step without further purification. IR (cm^{-1}): 3032, 2929, 2119, 1640, 1589, 1487, 1332, 1290, 1093, 1016, 1003, 827, 739, 699. ^{1}H-NMR (DMSO-d_6) δ: 8.20 (s, 1H, 6-H), 7.47 (s, 4H, phenyl-H), 7.34–7.30 (m, 5H, phenyl-H), 5.27 (s, 2H, CH_2). ^{13}C-NMR (DMSO-d_6) δ: 158.5, 139.2, 136.6, 133.3, 132.1, 131.8, 129.3, 128.4, 128.0, 127.7, 127.6, 123.6, 54.5.

2-Methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (9a).[21,24]

A solution of **8a** (227 mg, 1 mmol) in dry DMF (15 mL) was stirred at 130°C for 4 h. The solvent was removed under reduced pressure and the residue was recrystallized from EtOH to give **9a** (160 mg; 80%) as pale yellow crystals, mp 307–308°C (lit.[21]: 312–313°C). MS: m/z (rel. int.) 199 (M^+, 37%), 128 (100), 115 (85), 114 (40), 89 (33), 77 (33), 63 (37), 56 (36). IR (cm^{-1}): 3437, 3178, 2941, 1632, 1550, 1450, 1413, 1384, 1330, 1233, 1075, 998, 889, 841, 781, 734, 696, 642, 578. ^{1}H-NMR (DMSO-d_6) δ: 12.20 (s, 1H, NH), 8.38 (s, 1H, 4-H), 8.20–8.16 (m, 1H, 9-H), 7.68–7.63 (m, 1H, 6-H), 7.51–7.44 (m, 1H, 7-H), 7.35–7.29 (m, 1H, 8-H), 3.78 (s, 3H, CH_3). ^{13}C-NMR (DMSO-d_6) δ: 158.2, 138.3, 136.5, 126.9, 126.2, 122.1, 121.6, 121.5, 112.5, 111.3, 38.5.

2-Benzyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (9b).

A solution of **8b** (303 mg, 1 mmol) in dry DMF (15 mL) was stirred at 130°C for 5 h. The solvent was removed under reduced pressure and the residue was recrystallized from EtOH to give **9b** (267 mg; 97%) as pale yellow crystals, mp 284–285°C. *Anal.* Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 73.91; H, 5.02; N, 15.32. MS: m/z (rel. int.) 275 (M^+, 96%), 171 (90), 143 (54), 128 (76), 106 (84), 101 (65), 91 (100), 65 (43). IR (cm^{-1}): 3447, 3174, 3081, 2957, 1630, 1545, 1450, 1398, 1330, 1239, 1218, 1161, 1075, 814, 781, 752, 698, 648, 606, 532. ^{1}H-NMR (DMSO-d_6) δ: 12.28 (s, 1H, NH), 8.45 (s, 1H, 4-H), 8.21–8.17 (m, 1H, 9-H), 7.68–7.64 (m, 1H, 6-H), 7.52–7.45 (m, 1H, 7-H), 7.36–7.23 (m, 6H, 8-H, phenyl-H), 5.42 (s, 2H, CH_2). ^{13}C-NMR (DMSO-d_6) δ: 158.0, 138.3, 137.9, 136.4, 128.3, 127.7, 127.6, 127.2, 126.3, 122.2, 121.6, 112.6, 111.4, 53.0.

2-Benzyl-7-chloro-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (9c).

A solution of **8c** (169 mg, 0.5 mmol) in dry DMF (10 mL) was stirred at 130°C for 10 h. The solvent was removed under reduced pressure and the residue was recrystallized from EtOH to give **9c** (147 mg; 95%) as colorless crystals, mp 289–291°C. *Anal.* Calcd for $C_{17}H_{12}N_3OCl$: C, 65.92; H, 3.90; N, 13.57. Found: C, 65.77; H, 4.18; N, 13.26. MS: m/z (rel. int.) 311 (M^+, 26%), 309 (M^+, 76), 207 (23), 205 (78), 179 (9), 177 (26), 164 (8), 162 (23), 142 (12), 127 (16), 106 (100), 91 (45), 65 (15). IR (cm^{-1}): 3097, 3035, 2921, 1628, 1544, 1455, 1398, 1331, 1234, 1051, 910, 805, 698. ^{1}H-NMR (DMSO-d_6) δ: 12.37 (br s, 1H, NH), 8.45 (s, 1H, 4-H), 8.14 (d, J = 8.4 Hz, 1H, 9-H), 7.72 (d, J = 1.5 Hz, 6-H), 7.34 (dd, J = 8.4 Hz, 1.5 Hz, 1H, 8-H), 7.31–7.23 (m, 5H, phenyl-H), 5.40 (s, 2H, CH_2). ^{13}C-NMR (DMSO-d_6) δ: 157.8, 138.8, 137.8, 137.1, 130.8, 128.4, 127.7, 127.2, 122.9, 122.1, 121.0, 112.4, 111.3, 53.0.

2-Methyl-5-propyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (10a).

A suspension of **9a** (199 mg, 1 mmol), K_2CO_3 (280 mg, 2 mmol), and 1-iodopropane (2 mL, 20 mmol) in DMF (10 mL) was stirred at rt for 65 h. It was then evaporated to dryness under reduced pressure and the residue was taken up in water (20 mL). The solid material was collected by filtration and recrystallized from EtOH to give **10a** (157 mg; 65%) as pale yellow crystals, mp 104–105°C. *Anal.* Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.51; H, 6.29; N, 17.22. MS: m/z (rel. int.) 241 (M^+, 100%), 213 (50), 212 (97), 184 (24), 183 (33), 143 (23), 128 (33), 44 (29). IR (cm^{-1}): 3442, 2963, 2937, 2875, 1651, 1452, 1382, 1327, 1200, 1048, 1005, 883, 780, 752, 678. ^{1}H-NMR (DMSO-d_6) δ: 8.65 (s, 1H, 4-H), 8.23–8.19 (m, 1H, 9-H), 7.78–7.74 (m, 1H, 6-H), 7.55–7.48 (m, 1H, 7-H), 7.38–7.30 (m, 1H, 8-H), 4.44 (t, J = 7.0 Hz, 2H, $NC\underline{H}_2CH_2CH_3$), 3.78 (s, 3H, NCH_3), 1.86–1.73 (m, 2H, $NCH_2C\underline{H}_2CH_3$), 0.82 (t, J = 7.5 Hz, 3H, $NCH_2CH_2C\underline{H}_3$). ^{13}C-NMR (DMSO-$d_6$) δ: 157.9, 138.6, 137.0, 126.2, 125.7, 121.9, 121.8, 121.7, 111.0, 110.5, 44.6, 38.5, 22.6, 10.9.

2-Benzyl-5-propyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (10b).

A suspension of **9b** (275 mg, 1 mmol), K_2CO_3 (280 mg, 2 mmol), and 1-iodopropane (1 mL, 10 mmol) in DMF (10 mL) was stirred at rt for 65 h. It was then evaporated under reduced pressure and the residue was taken up in water (20 mL). The solid material was collected by filtration and recrystallized from EtOH to give **10b** (279 mg; 88%) as pale yellow crystals, mp 150–151°C. *Anal.* Calcd for $C_{20}H_{19}N_3O \cdot 0.2\ H_2O$: C, 74.84; H, 6.09; N, 13.09. Found: C, 74.96; H, 5.99; N, 13.11. MS: m/z (rel. int) 317 (M^+, 87%), 213 (71), 184 (77), 183 (84), 128 (82), 106 (47), 101 (48), 91 (100). IR (cm^{-1}): 3446, 2961, 1660, 1551, 1452, 1320, 1196, 1074, 1060, 1018, 748, 700, 545. ^{1}H-NMR (DMSO-d_6) δ: 8.72 (s, 1H, 4-H), 8.25–8.20 (m, 1H, 9-H), 7.80–7.75 (m, 1H, 6-H), 7.56–7.49 (m, 1H, 7-H), 7.39–7.33 (m, 1H, 8-H), 7.33–7.23 (m, 5H, phenyl-H), 5.42 (s, 2H, $PhC\underline{H}_2$), 4.45 (t, J = 7.0 Hz, 2H, $NC\underline{H}_2CH_2CH_3$), 1.87–1.74 (m, 2H, $NCH_2C\underline{H}_2CH_3$), 0.83 (t, J

= 7.2 Hz, 3H, $NCH_2CH_2C\underline{H}_3$). ^{13}C-NMR (DMSO-$d_6$) δ: 157.7, 138.7, 137.8, 136.9, 128.3, 127.7, 127.2, 126.5, 126.4, 122.0, 121.9, 121.8, 111.1, 110.7, 53.0, 44.7, 22.7, 11.0.

5-Propyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (11).

To a suspension of $AlCl_3$ (532 mg, 4 mmol) in dry toluene (40 mL) was added **10b** (317 mg, 1 mmol). The mixture was stirred at 80°C for 2 h. It was then evaporated to dryness under reduced pressure, the residue was treated with water (20 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to afford **11** (182 mg; 80%) as reddish crystals, mp 252–253°C (CH_2Cl_2). *Anal.* Calcd for $C_{13}H_{13}N_3O$: C, 68.71; H, 5.77; N, 18.49. Found: C, 68.71; H, 6.04; N, 18.24. MS: m/z (rel. int.) 228 (10%), 227 (M^+, 65), 199 (14), 198 (100), 128 (17), 115 (15), 114 (13), 101 (16). IR (cm^{-1}): 3445, 3162, 3074, 3010, 2950, 2876, 1645, 1528, 1451, 1409, 1341, 1322, 1268, 1022, 854, 781, 763, 563. ^{1}H-NMR (DMSO-d_6) δ: 12.70 (s, 1H, NH), 8.66 (s, 1H, 4-H), 8.19 (d, J = 7.5 Hz, 1H, 9-H), 7.78 (d, J = 8.4 Hz, 1H, 6-H), 7.55–7.49 (m, 1H, 7-H), 7.38–7.32 (m, 1H, 8-H), 4.47 (t, J = 6.9 Hz, 2H, $NC\underline{H}_2CH_2CH_3$), 1.87–1.74 (m, 2H, $NCH_2C\underline{H}_2CH_3$), 0.83 (t, J = 7.3 Hz, 3H, $NCH_2CH_2C\underline{H}_3$). ^{13}C-NMR (DMSO-$d_6$) δ: 159.2, 138.3, 137.3, 126.6, 126.1, 121.9, 121.8, 111.1, 110.8, 44.7, 22.7, 11.0.

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