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Unexpected Formation of 4-aryl-1-(Propane-2-ylidenehydrazono)-2,3-diazaspiro[5.5]undec-3-ene by the Reaction of Pyridazinethiones Derivatives with Hydrazine

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Abstract: After making a new series of spiro[cycloalkane]pyridazinones with high Fsp^3 character available, the new target was to synthesize derivatives comprising nitrogen-containing heterocycles, such as triazolo or tetrazolo rings. The corresponding thioxo derivatives (**1a**,**b**) seemed to be good starting materials for the synthesis of tetrazolo derivatives. The reaction of the pyridazinethiones (**1a**,**b**) with hydrazine surprisingly resulted in Schiff bases (**3a**,**b**) deriving from the reaction of hydrazones (**2a**,**b**) with acetone.

Keywords: pyridazinethione; spiro[cycloalkane]pyridazine; hydrazine; acetone; Schiff base

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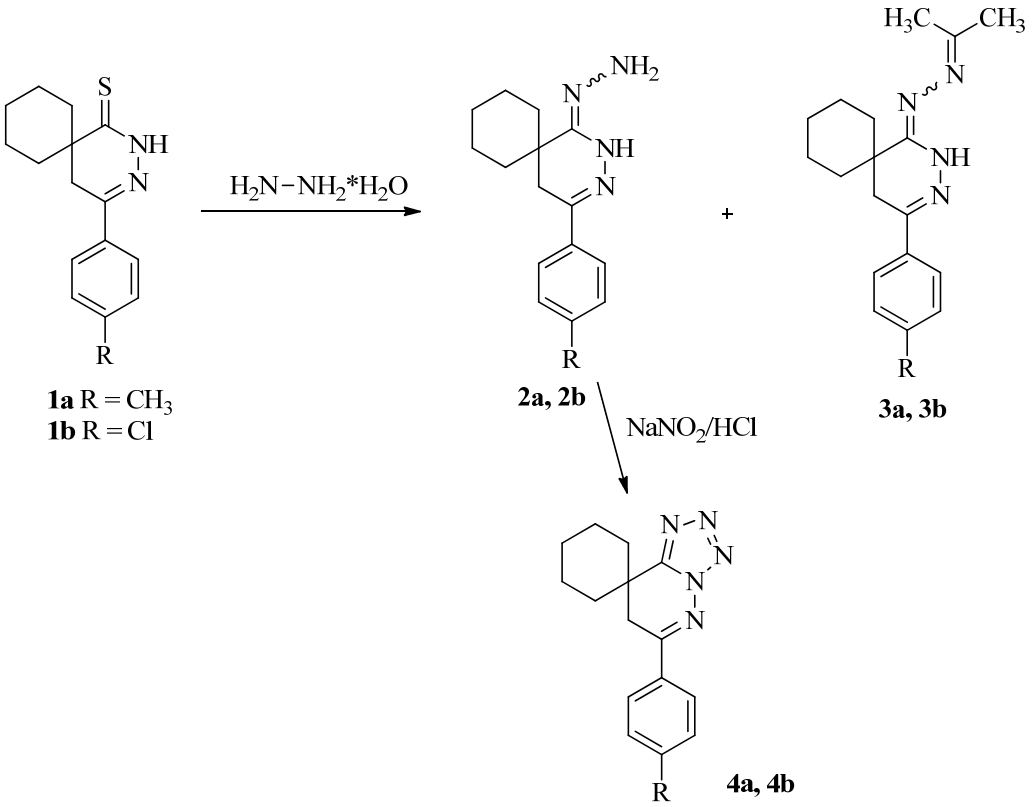
1. Introduction

The molecule bank of a company might play an important role in the early phase of preclinical drug discovery. To find a hit, a high-throughput screening (HTS) campaign may be a useful tool [1]. In the design of new compounds for a molecule bank, the application of some widely used rules (Lipinski rule of five, Veber's rule) [2–4] and other concepts of medicinal chemistry, such as the role of aromatic rings or bioisosteric nitrogen-containing heterocycles, are of key importance [5–8]. Lovering introduced the Fsp^3 character, which usually shows a good correlation with logP and other physicochemical parameters [9,10]. With the consideration of the above aspects, a series of spiro[cycloalkane]pyridazinones with high Fsp^3 character and advantageous physicochemical parameters was synthetized [11–13]. Starting from 2-oxaspiro[4.4]nonane-1,3-dione and 2-oxaspiro[4.5]-1,3-dione, the ketocarboxylic acids were obtained by Friedel-Crafts or Grignard reaction. The ring closure took place with hydrazine or its derivatives: methylhydrazine and phenylhydrazine. A few of the obtained dihydropyridazine derivatives were alkylated. The corresponding pyridazinonethiones (**1**) were prepared by the reaction of pyridazinones with phosphorus pentasulfide [14] (Scheme 1).



Scheme 1. Synthesis of hydrazone and tetrazolo derivatives starting from spiro[cycloalkane]pyridazinethiones.

2. Results and Discussion

We wanted to extend this compound family with further examples, combining the spiro[cycloalkane]pyridazines with nitrogen-containing heterocycles, such as triazole or tetrazole. The hydrazone derivatives of **1a,b** may be important intermediates for the synthesis of tetrazoles. To obtain these compounds, the reaction of pyridazinethiones (**1a** and **1b**) with hydrazine in tetrahydrofuran was studied [14]. In the case of the chloro and methyl derivatives, the *E* and *Z* stereoisomers of the desired hydrazones (**2a** (R = CH_3, yield: 59%) and **2b** (R = Cl, yield:61%)) were obtained surprisingly with a small amount of a side product (**3a** and **3b**), which is the Schiff base of the expected hydrazones with acetone (**3a,b**). The structures of the isolated by-products were established by detailed ^{1}H and ^{13}C NMR and HRMS studies. The hydrazones (**2a** R = CH_3 and **2b** R = Cl) might have been the intermediates, which reacted with the trace amount of acetone present in the glassware. Reacting the hydrazones (**2a** R = CH_3 and **2b** R = Cl) with sodium nitrite, the corresponding tetrazole derivatives (**4a** R = CH_3 and **4b** R = Cl) were obtained smoothly [14]. According to the database SciFinder, the compounds **3a** and **3b** (R = CH_3, Cl) are new compounds, which may be valuable members of a molecule bank. Table 1 summarizes the most important physicochemical parameters of **3a,b**. Interestingly the Fsp^3 character of compounds **3a,b** is high, but the logP and clogP values (4.6–5.2) are not advantageous enough.

Table 1. The physicochemical parameters of the hydrazone derivatives.

Starting Material	R^1	Product	Fsp^3	LogP	ClogP	TPSA
1a	CH_3	**3a**	0.53	4.59	5.03	49.11
1b	Cl	**3b**	0.50	4.66	5.24	49.11

3. Materials and Methods

3.1. General Information, TLC, Preparative TLC

Hydrazine hydrate [10217-52-4], tetrahydrofuran [109-99-9], dichloromethane [75-09-2], heptane [142-82-5], methanol [67-56-1] were purchased from SigmaAldrich. TLC was carried out using Kieselgel 60 F_{254} (Merck 1.05554.0001). The analytical samples for NMR and HRMS studies were purified by preparative TLC using Kieselgel 60 F_{254} (Merck 1.07748.1000) coated glass plates.

3.2. NMR Spectroscopy

NMR measurements were performed on a Varian VNMRS 400 MHz NMR spectrometer equipped with a ^{15}N-^{31}P{^{1}H-^{19}F} 5 mm OneNMR room temperature probe, a Varian VNMRS 500 MHz NMR spectrometer equipped with a ^{1}H {^{13}C/^{15}N} 5 mm PFG Triple Resonance ^{13}C Enhanced Cold Probe, a Varian VNMRS 800 MHz NMR spectrometer equipped with a ^{1}H{^{13}C/^{15}N} TripleResonance^{13}C Enhanced Salt Tolerant Cold Probe (Varian, Inc., Palo Alto, CA, USA), a Bruker Avance III HDX 500 MHz NMR spectrometer equipped with a ^{1}H {^{13}C/^{15}N} 5 mm TCI CryoProbe, and a Bruker Avance III HDX 500 MHz NMR spectrometer equipped with a ^{1}H-^{19}F{^{13}C/^{15}N} 5 mm TCI CryoProbe (Bruker Corporation, Billerica, MA, USA). ^{1}H and ^{13}C chemical shifts are given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) (^{1}H, ^{13}C) or dimethylsulfoxide-d_6(^{13}C) as the internal standard (0.00 ppm and 39.4 ppm, respectively). ^{1}H-^{1}H, direct ^{1}H-^{13}C, and long-range ^{1}H-^{13}C scalar spin–spin connectivity were established from 2D COSY, TOCSY, HSQC, and HMBC experiments. ^{1}H-^{1}H spatial proximities were determined using two-dimensional NOESY or ROESY experiments. ^{15}N Chemical shifts are referenced to nitromethane (0.0 ppm) and are obtained from ^{1}H-^{15}N HMBC measurements. All pulse sequences were applied by using the standard spectrometer software package. All experiments were performed at 298 K. NMR spectra were processed using VnmrJ 2.2 Revision C (Varian, Inc. Palo Alto, CA, USA), Bruker TopSpin 3.5 pl 6 (Bruker Corporation, Billerica, MA, USA), and ACD/Spectrus Processor version 2017.1.3 (Advanced Chemistry Development, Inc., Toronto, ON, Canada).

3.3. Mass Spectrometry

HRMS and MS-MS analyses were performed on a ThermoVelos Pro Orbitrap Elite (Thermo Fisher Scientific) system. The ionization method was ESI operated in positive ion mode. The protonated molecular ion peaks were fragmented by CID at a normalized collision energy of 35%. For the CID experiment, helium was used as the collision gas. The samples were dissolved in methanol. Data acquisition and analysis were accomplished with Xcalibur software version 2.0 (Thermo Fisher Scientific, Waltham, MA, USA).

*3.4. General Procedure for the Preparation of 1-(Propane-2-ylidenehydrazono)-4-(p-substituted phenyl)-2,3-diazaspiro[5.5]undec-3-ene (**3a**,**3b**)*

The hydrazine monohydrate (0.10 mL, 1.2 mmol) was dissolved in THF (5 mL), and then the corresponding pyridazinethione derivatives (**1a,b**) (0.40 mmol) were also dissolved in THF (15 mL) and added dropwise to the hydrazine solution. The reaction mixture was stirred at reflux for 12 h, and then the solvent was evaporated. The residue was dissolved in dichloromethane (20 mL) and washed with distilled water (2 × 10 mL). The organic layer was dried over $MgSO_4$, filtered and evaporated. The crude productwas purified by preparative thin-layer chromatography (eluent: heptane:dichloromethane:methanol/5:5:1) to give by-products and hydrazone derivatives.

1-(Propan-2-ylidenehydrazono)-4-(p-tolyl)-2,3-diazaspiro[5.5]undec-3-ene (**3a**) Yield: 14%;Rf(heptane:dichloromethane:methanol/5:5:1) = 0.48,^{1}H NMR (499.9 MHz; DMSO-d_6) δ = 1.31–1.71 (m, 10H, cyclohexyl); 1.94 (s, 3H, H-3′); 1.97 (s, 3H, H-1′); 2.37 (s, 3H, C(4″)-CH_3); 2.72 (s, 2H, H-5); 7.22 (m, 2H, H-3″, H-5″); 7.67 (m, 2H, H-2″, H-6″); 9.75 (br s, 1H, NH-2) ppm; ^{13}C NMR (125.7 MHz; DMSO-d_6) δ = 17.52 (C-3′); 20.72 (C-4″-CH3); 20.97 (C-8, C-10); 25.51 (C-9); 27.77 (C-1′); 30.75 (C-5); 32.75 (C-7, C-11); 33.31 (C-6); 124.88

(C-2″, C-6″); 128.98 (C-3″, C-5″); 134.32 (C-1″); 134.32 (C-4″); 145.67 (C-4); 153.55 (C-1), 160.79 (C-2′) ppm; ^{15}N NMR (40.5 MHz; DMSO-d_6) δ = −333.48 (N-2′); −306.25 (N-3); −145.69 (N-2); (N-1) ppm; HRMS: M + H = 311.22313 (delta = 0.3 ppm; $C_{19}H_{27}N_4$). MS-MS (CID = 35%; rel. int. %): 282(100); 267(31); 255(13); 239(24); 227(8); 212(39); 199(10); 186(3); 138(2).

4-(4-Chlorophenyl)-1-(propan-2-ylidenehydrazono)-2,3-diazaspiro[5.5]undec-3-ene (**3b**) Yield: 7%; ^{1}H NMR (499.9 MHz; DMSO-d_6) δ = 1.31–1.71 (m, 10H, cyclohexyl); 1.94 (s, 3H, H-3′); 1.97 (s, 3H, H-1′); 2.74 (s, 2H, H-5); 7.46 (m, 2H, H-3″, H-5″); 7.80 (m, 2H, H-2″, H-6″); 9.90 (s, 1H, NH-2) ppm; ^{13}C NMR (125.7 MHz; DMSO-d_6) δ = 17.55 (C-3′); 20.93 (C-8, C-10); 24.77 (C-1′); 25.50 (C-9); 30.68 (C-5); 32.78 (C-7, C-11); 33.20 (C-6); 126.65 (C-2″, C-6″); 128.40 (C-3″, C-5″); 133.00 (C-4″); 135.93 (C-1″); 144.31 (C-4); 153.10 (C-1), 161.10 (C-2′) ppm; ^{15}N NMR (40.5 MHz; DMSO-d_6) δ = −333.80 (N-2′); −309.88 (N-3); −267.65 (N-1′); −147.14 (N-2) ppm; HRMS: M + H = 331.16715 (delta = −3.8 ppm; $C_{18}H_{24}N_4Cl$). HR-ESI-MS-MS (CID = 45%; rel. int. %): 302(100); 301(17); 287(30); 275(10); 261(12); 259(17); 247(10); 232(33).

4. Conclusions

Reacting spiro[cycloalkane]pyridazinethiones with hydrazine in tetrahydrofuran, the desired hydrazones and, surprisingly, their Schiff bases with acetone were obtained. The hydrazones might have reacted with the acetone present in the glassware. The structures of the isolated *p*-substituted 4-aryl-1-(propane-2-ylidenehydrazono)-2,3- diazaspiro[5.5]undec-3-enes (**3a**,**3b**) have been fully characterized by ^{1}H, ^{13}C, ^{15}N NMR and HRMS.

Supplementary Materials: The following are available online: HRMS, ^{1}H, and ^{13}C NMR spectra of **3a,b**.

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