Pyridazines. L [1]. Syntheses and Reactions of Phenyl(3-pyridazinyl)methane Derivatives

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Received April 17, 1989

A convenient approach to phenyl (3-pyridazinyl) ketone (**6**) and phenyl(3-pyridazinyl)methanol (**7**) is proposed. Reactions of the related diarylmethyl chloride **8** with various *N*- and *S*-nucleophiles were found to afford the expected amines **9a-c**, **10a-c** and thioethers **11a,b** in satisfactory yields.

J. Heterocyclic Chem., **26**, 1787 (1989).

Since the diphenylmethane system is abundant in various pharmacologically active compounds, much effort has been devoted to the search for synthetic routes providing access also to analogues thereof in which one or both of the phenyl moieties are replaced by a heteroaromatic system [2,3]. In continuation of our studies in the field of diazole- and diazine-derived isosters [4-10] of benzophenone and benzhydrol we want to report here on investigations aimed at the development of convenient syntheses of phenyl (3-pyridazinyl) ketone (**6**), phenyl(3-pyridazinyl)-methanol (**7**) and the corresponding diarylmethyl chloride **8** as well as on reactions of the latter with selected *N*- and *S*-nucleophiles. Whereas the chemistry of aryl (4-pyridazinyl) ketones and the related alcohols has been investigated in some detail [5-9], so far there is only a report in the patent literature [11] on the 3-pyridazinyl-derived congeners **6**, **7** [12]. Considering that phenyl (4-pyridazinyl) ketone can be prepared in satisfactory yield by selenium dioxide oxidation of 4-benzylpyridazine [5], 3-benzylpyridazine (**3**) [11] was subjected to these conditions and a 85% yield of the ketone **6** was obtained.

This approach, however, suffers from difficulties encountered in the preparation of **3**. We did not succeed in obtaining the latter compound in yields exceeding 40% *via* the route displayed in Scheme 1 [13], since **2** upon treatment with hydrazine hydrochloride in 1-propanol/-sodium pyrophosphate buffer (*p*H 6.5) affords substantial amounts (up to 40%) of a side product **4**, which obviously is formed *via* intramolecular dismutation of the dihydrofuran derivative **2**. Assignment of the 4,5-dihydro-6-benzylpyridazin-3(2*H*)-one structure is based on elemental analyses, ms molecular-weight determination and spectral data [16].

Based on the recently reported [17] convenient synthesis of 3-pyridazinecarbonitrile (**5**), a more effective route (also permitting large scale preparation of the target ketone **6**) was developed which is characterized by reaction of **5** with phenylmagnesium chloride. Whereas this procedure gives a 59% yield of phenyl (3-pyridazinyl) ketone, attempted employment of phenyllithium only afforded traces of **6** due to predominant attack at the heteroaromatic system. Preparation of the benzhydrol analogue **7** then was achieved almost quantitatively by reduction of **6** employing sodium borohydride.

Transformation of the alcohol **7** into the diarylmethyl halide **8** was found not to require initial protonation of **7** as described in ref [11], but could be accomplished in 84% yield by simply reacting the alcohol with thionyl chloride in toluene at room temperature.

In previous investigations [8] it has been demonstrated

Scheme 1

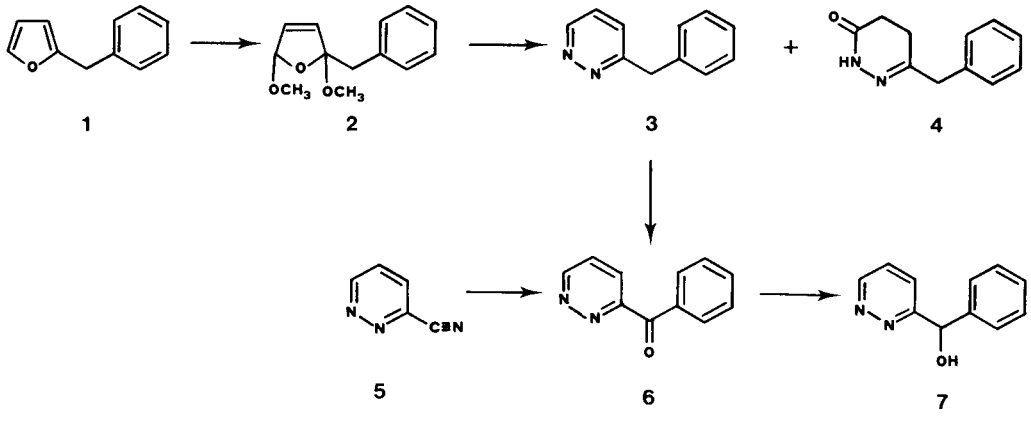


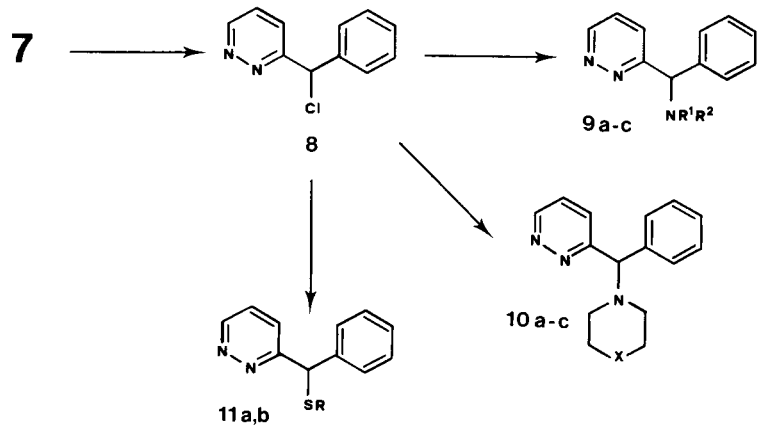
Table 1

Yields and Analytical Characterisation of Compounds **9a-c**, **10a-c** and **11a,b**

Compound No.	Yield (%)	mp (°C)	Molecular Formula (MW)	Elemental Analyses (%) (Calcd./Found) C	H	N	^{1}H-NMR (deuteriochloroform) δ (ppm) Pyridazine H-6	Pyridazine H-4, H-5 Phenyl-H	Benzylic H	Other Protons
9a	69	140-141	$C_{17}H_{15}N_3$ 261.33	77.60 [a] 77.54	5.82 5.83	15.97 15.95	9.14 (dd, 1H)	6.59-7.69 (m,12H)	5.86 (d,1H)	5.57 (s, broad, NH, exchangeable with D_2O, 1H)
9b	75	103-105	$C_{18}H_{17}N_3$ 275.36	77.50 [b] 77.50	6.29 6.22	15.06 15.03	9.12 (dd, 1H)	6.69-7.60 (m,12H)	6.46 (s,1H)	2.81 (s, CH_3, 3H)
9c	65	159-160	$C_{15}H_{17}N_3$ 239.32	75.28 75.16	7.16 7.18	17.56 17.38	9.01 (dd, 1H)	7.08-7.89 (m, 7H)	4.80 (s,1H)	2.10-2.75 (m, pyrrolidine H-2, H-5, 4H) 1.60-1.90 (m, pyrrolidine H-3 H-4, 4H)
10a	71	165-166	$C_{16}H_{19}N_3$ 253.35	75.85 75.60	7.56 7.60	16.59 16.49	9.00 (dd, 1H)	7.15-7.85 (m, 7H)	4.81 (s,1H)	2.08-2.58 (m, piperidine H-2, H-6, 4H) 1.35-1.75 (m, piperidine H-3, H-4, H-5, 6H)
10b	59	137-138	$C_{15}H_{17}N_3O$ 255.32	69.58 [c] 69.45	6.77 6.58	16.23 16.12	9.08 (dd, 1H)	7.20-7.89 (m, 7H)	4.85 (s,1H)	3.69-3.82 (m, morpholine-H α to O, 4H) 2.16-2.70 (m, morpholine-H α to N, 4H)
10c	73	153-154	$C_{16}H_{20}N_4$ 268.36	71.61 71.55	7.51 7.57	20.88 20.74	9.05 (dd, 1H)	7.18-7.85 (m, 7H)	4.87 (s,1H)	2.35-2.70 (m, piperazine H, 8H) 2.27 (s, CH_3, 3H)
11a	71	152-153	$C_{17}H_{14}N_2S$ 278.38	73.35 73.19	5.07 5.09	10.06 10.21	9.05 (dd, 1H)	7.13-7.87 (m,12H)	6.02 (s,1H)	
11b	65	62-64	$C_{15}H_{19}N_3S$ 273.40	65.90 65.78	7.00 7.06	15.37 14.92	9.08 (dd, 1H)	7.15-7.80 (m, 7H)	5.63 (s,1H)	2.45-2.90 (m, CH_2-CH_2, 4H) 2.20 (s, CH_3, 3H)

[a] Calcd. for $C_{17}H_{15}N_3 \cdot 1/10H_2O$.
[b] Calcd. for $C_{18}H_{17}N_3 \cdot 1/5H_2O$.
[c] Calcd. for $C_{15}H_{17}N_3O \cdot 1/5H_2O$.

Scheme 2



9a R^1= Ph R^2= H 9b R^1= Ph R^2= CH_3 9c R^1, R^2= -$(CH_2)_4$- 10a X= CH_2

10b X= O 10c X= NCH_3 11a R= Ph 11b R= $(CH_2)_2N(CH_3)_2$

that 4-α-chlorobenzylpyridazine upon treatment with secondary aliphatic amines not only gives the usual 4-α-aminobenzylpyridazines, but additionally affords up to 20% of isomeric tele-substitution products (4-benzyl-5-aminopyridazines). In contrast, 3-α-chlorobenzylpyridazine (**8**) now was found not to be attacked by nitrogen nucleophiles at the heteroaromatic system, but exclusively at the benzylic carbon atom (analysis of the reaction mixtures by tlc). Thus, by reaction of **8** with aniline, *N*-methylaniline or various cycloamines, respectively, reasonable yields of 3-α-aminobenzylpyridazines **9a-c** and **10a-c** were obtained (Scheme 2). Compound **10c** was prepared in view of the isosterism with cyclizine, a potent antihistaminic agent [2], which (like several of its heteroaromatic analogues) also has been found to exhibit hypolipidemic activity [18].

Likewise, a pronounced regioselectivity was observed in reactions of **8** with *S*-nucleophiles. According to chromatographic and ^{1}H-nmr spectroscopic investigations of the reaction products obtained upon treatment of **8** with sodium thiophenolate or sodium 2-dimethylaminothioethanolate in toluene, also in this case the nucleophile does not attack the pyridazine ring. Thus, analytically pure thioethers **11a,b** could be obtained in satisfactory yields. Compound **11b** appears to be of interest due to its structural relation to the antihistaminic and hypnotic agent diphenhydramine [2]. Structure proof of all newly synthesized compounds rests on elemental analysis together with spectroscopic data (Table 1). An unequivocal proof for the position of the *N*- or *S*-substituent in compounds **9a-c**, **10a-c** and **11a,b** is provided by the characteristic pattern of the pyridazine H-6 signal since the latter in all ^{1}H-nmr spectra is well separated from the signals of other aromatic protons.

Investigations with regard to the reactivity of 3-α-chlorobenzylpyridazine towards *O*-nucleophiles are in progress, the results will be published elsewhere.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage microscope and are uncorrected. The ir spectra (potassium bromide) were recorded on a Jasco IRA-1 spectrometer. The glc/ms analyses were carried out on a Hewlett-Packard 5890A/5970B-GC/MSD instrument. The ^{1}H-nmr spectra were obtained on a Varian EM 390 (90 MHz), the ^{13}C-nmr spectrum was recorded on a Bruker AC 80 (20.15 MHz). Chemical shifts are reported in ppm downfield from TMS as an internal standard and are given in δ units. For analytical tlc, DC-Alufolien, Kieselgel 60 F_{254} (Merck) were used. Column chromatography was performed on Kieselgel 60 (70-230 mesh; Merck). Elemental analyses were carried out by Mikroanalytisches Laboratorium (Dr. J. Zak), Institute of Physical Chemistry, University of Vienna.

2-Benzyl-2,5-dimethoxy-2,5-dihydrofuran (**2**).

A solution of 2-benzylfuran (1.58 g, 10 mmoles) [14] and sodium bromide (0.51 g, 5 mmoles) in methanol (30 ml) was placed in a recipient equipped with two glass-carbon electrodes (contact surface approximately 100 cm²) and a magnetic stirrer. The electrochemical oxidation was carried out at −5° by applying a 12 V (0.6 A) current for 6 hours. Then methanol was evaporated *in vacuo* and the residue was distilled in a Kugelrohr apparatus at 130°/0.2 mbar to yield 1.87 g (85%) of pure **2** (glc/ms analysis).

Reaction of **2** with Hydrazine Hydrochloride.

A mixture of **2** (2.20 g, 10 mmoles), hydrazine hydrochloride (0.68 g, 10 mmoles), 1-propanol (30 ml) and sodium pyrophos-

phate buffer solution (30 ml, *p*H 6.5) was refluxed for 10 hours under argon atmosphere. Then the reaction mixture was extracted exhaustively with dichloromethane. The combined organic layers were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was submitted to column chromatography [ethyl acetate:dichloromethane (2:1)] to yield fraction A: 4,5-dihydro-6-benzylpyridazine-3(2*H*)-one (**4**) (0.66 g, 35%) and fraction B: 3-benzylpyridazine (**3**) (0.68 g, 40%) [11].

4,5-Dihydro-6-benzylpyridazine-3(2*H*)-one (**4**).

This compound was obtained as colourless crystals from ethanol, mp 94°; ^{1}H-nmr (deuteriochloroform): δ 2.40 (s, CH_2–CH_2, 4H), 3.65 (s, benzylic H, 2H), 7.31 (m, phenyl H, 5H), 8.70 (s, broad, NH, exchangeable with deuterium oxide, 1H); ir: 1660 cm^{-1} (C=O), 3200 cm^{-1} (NH); ms: m/e 188 (M^+, 100), 117 (23), 91 (51).

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.42; H, 6.42; N, 14.78.

3-Benzylpyridazine (**3**).

This compound was obtained as light yellow oil (ref [11]: mp 65-67°); ^{1}H-nmr (deuteriochloroform): δ 4.38 (s, benzylic H, 2H), 7.10-7.45 (m, phenyl H, pyridazine H-4, H-5, 7H), 9.10 (dd, pyridazine H-6); ms: m/e 170 (M^+, 23), 169 (100), 115 (21).

Phenyl (3-Pyridazinyl) Ketone (**6**).

Method A.

A solution of **3** (1.70 g, 10 mmoles) in glacial acetic acid (55 ml) was added dropwise to a stirred suspension of selenium dioxide (1.21 g, 11 mmoles) in glacial acetic acid (55 ml). After heating to 100° for 1 hour, the mixture was filtered, the ice-cooled filtrate was made alkaline by addition of 50% aqueous sodium hydroxide and was then extracted with dichloromethane. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed *in vacuo*. Recrystallisation of the residue from water/ethanol gave **6** (1.56 g, 85%) as colourless crystals, mp 69-70° (ref [11] 70-71°); ^{1}H-nmr (deuteriochloroform): δ 7.30-7.90 (m, phenyl H-3, H-4, H-5, pyridazine H-5, 4H), 8.10-8.35 (m, phenyl H-2, H-6, pyridazine H-4, 3H), 9.40 (dd, pyridazine H-6); ir: 1655 cm^{-1} (C=O); ms: m/e 184 (M^+, 27), 156 (100), 105 (66), 77 (81), 51 (32).

Method B.

To a solution of pyridazine-3-carbonitrile (**5**) [17] (1.05 g, 10 mmoles) in a 1:1 mixture of dry diethyl ether and tetrahydrofuran (20 ml), a 2*M* phenylmagnesium chloride solution in tetrahydrofuran (5.5 ml, 11 mmoles) was added at −10° under argon atmosphere within 15 minutes. Then the reaction mixture was allowed to warm up to room temperature and stirring was continued for 2 hours. After quenching with 2*N* hydrochloric acid (10 ml), the organic layer was separated and the aqueous layer was extracted exhaustively with dichloromethane. The combined organic extracts were washed with water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was passed through a short column using ethyl acetate as the eluent to yield 1.09 g (59%) of pure (glc/ms analysis) **6**.

Phenyl(3-pyridazinyl)methanol (**7**).

To a solution of **6** (1.84 g, 10 mmoles) in methanol (50 ml), sodium borohydride (0.10 g, 2.5 mmoles) was added within 15 minutes and the mixture was stirred at room temperature for 1 hour. Then it was acidified with 2*N* sulfuric acid and methanol was removed *in vacuo*. The ice-cooled solution was made alkaline by addition of 50% aqueous sodium hydroxide and was then extracted exhaustively with dichloromethane. The organic extracts were dried over anhydrous sodium sulfate and were then evaporated *in vacuo*. The residue was recrystallized from ethanol to give **7** (1.77 g, 95%) as colourless crystals, mp 141-144°, (ref [11] mp 130-135°); ^{1}H-nmr (deuteriochloroform): δ 4.99 (s, broad, OH, 1H, exchangeable with deuterium oxide), 6.05 (s, benzylic H, 1H), 7.26-7.52 (m, phenyl H, pyridazine H-4, H-5, 7H), 9.10 (dd, pyridazine H-6, 1H); ir: 3165 cm^{-1} (OH); ms: m/e 186 (M^+, 100), 169 (51), 156 (32), 109 (28), 107 (29), 105 (39), 79 (39), 77 (80), 51 (41).

3-α-Chlorobenzylpyridazine (**8**).

To a suspension of **7** (1.86 g, 10 mmoles) in dry toluene (100 ml) thionyl chloride (2 ml) was added at 0° within 15 minutes. The mixture was allowed to warm up to room temperature and was stirred for 12 hours. Then excess thionyl chloride was destroyed by addition of a saturated aqueous sodium hydrogencarbonate solution at 0°. The aqueous layer was exhaustively extracted with dichloromethane, the combined organic extracts were dried over anhydrous sodium sulfate and then evaporated *in vacuo*. The residue was recrystallised from cyclohexane to yield **8** (1.72 g, 84%) as pale yellow needles, mp 102-107° (ref [11] mp 110-112°); ^{1}H-nmr (deuteriochloroform): δ 6.57 (s, benzylic H, 1H), 7.25-7.70 (m, phenyl H, pyridazine H-5, 6H), 7.74-7.90 (m, pyridazine H-4, 1H), 9.19 (dd, pyridazine H-6, 1H); ms: m/e 204, 206 (M^+, 3), 169 (100), 168 (24), 115 (23).

Reaction of 3-α-Chlorobenzylpyridazine with *N*-Nucleophiles.

General Procedure.

To a solution of **8** (103 mg, 0.5 mmole) in dry toluene (2 ml) the appropriate amine (5 mmoles) was added at room temperature. The mixture was refluxed for 6 hours under argon atmosphere. After cooling, excess amine and solvent were evaporated *in vacuo*. The residue was suspended in a minimum of water and the mixture was extracted exhaustively with dichloromethane. The organic extracts were dried over anhydrous sodium sulfate and were then evaporated *in vacuo*. The residue was passed through a short column using ethyl acetate as the eluent. The products obtained were recrystallized from cyclohexane. For yields, melting points, elemental analyses and ^{1}H-nmr data of compounds **9a-c** and **10a-c** see Table 1.

Reaction of 3-α-Chlorobenzylpyridazine with *S*-Nucleophiles.

General Procedure.

To a mixture of sodium hydride (80% in paraffin; 23 mg, 0.55 mmole) and dry toluene (2 ml), the appropriate thiole (0.55 mmole) was added under argon atmosphere. After stirring for 15 minutes, **8** (103 mg, 0.5 mmole) was added and the mixture was refluxed for 3 hours. After cooling, the solvent was removed *in vacuo*, the residue was suspended in a minimum of water and the mixture was extracted exhaustively with dichloromethane. The organic layer was dried over anhydrous sodium sulfate, evaporated *in vacuo* and the remaining residue was passed through a short column [eluent for **11a**, ethyl acetate; eluent for **11b**, light

petroleum:methanol:diethylamine (8:1:1)]. The products were recrystallized from cyclohexane. For yields, melting points, elemental analyses and ^{1}H-nmr data of compounds **11a,b** see Table 1.

Acknowledgement.

The authors wish to express their gratitude to the "Fonds zur Förderung der Wissenschaftlichen Forschung" for supporting this investigation (project P6260C). We are grateful to Dr. W. Holzer for recording the ^{13}C-nmr spectrum, to Doz. Dr. U. Jordis for valuable contributions with regard to the electrochemical preparation of compound **2** and to Mr. E. Möllner for recording the ir spectra.

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[12] According to ref [11] the alcohol **7** is obtained in $<20\%$ yield by reaction of 3-pyridazine carboxylic acid with benzaldehyde; oxidation of **7** by potassium permanganate to give **6** has been described [11], however, yields were not given.

[13] Treatment of 2-benzylfuran [14] with bromine in methanol solution has been proposed for the preparation of **2** [11] without yields reported. An electrochemical transformation of **1** into **2** developed in analogy to ref [15] now was found to give a 85% yield of **2** in a more convenient manner (see Experimental).

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[16] The appearance of a strong vibration band in the ir spectrum at 1660 cm^{-1} clearly indicates an oxo function being present. Besides the signals of the protons of the benzyl group, the ^{1}H-nmr spectrum (deuteriochloroform solution) of **4** exhibits a one-proton signal (disappearing upon addition of deuterium oxide) at 8.75 ppm attributable to a NH function and a four-proton singlet at 2.40 ppm originating from the protons attached to C-4 and C-5 of the heterocycle. In deuteriodimethylsulfoxide solution the latter protons form an AA'BB' system. The 4,5-dihydro-3(2*H*)-pyridazinone structure is further supported by the appearance of two CH_2 signals (δ = 25.90 ppm and δ = 23.78 ppm, respectively) and of a C=O signal (δ = 166.57 ppm) in the *J*-modulated ^{13}C-nmr spectrum (deuteriodimethyl sulfoxide solution).

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