Novel Diazinyl 3-Pyridyl Ketones: Efficient Synthesis and Complete Assignment of ^1H and ^{13}C NMR Spectra

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The preparation of six diazinyl 3-pyridyl ketones **3-8** is described. Detailed ^1H and ^{13}C nmr data of these novel building blocks are given.

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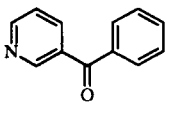
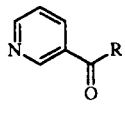
Introduction.

Phenyl-3-pyridylmethanone (**1**) represents an important building block for the construction of novel antithrombotic agents whose dual mode of action consists of inhibition of thromboxane A_2 synthetase and simultaneous blockade of thromboxane A_2 receptor [1,2]. Within a project directed towards bioisosteric modification of phenyl-3-pyridylmethanone derived antithrombotics we previously have elaborated convenient methods for the synthesis of aryl diazinyl methanones of type **2** [3-6]. In continuation of these studies we now became interested in diazinyl-3-pyridylmethanones **3-8** (see Scheme 1). Here we report on the synthesis of these novel ketones and on the complete assignment of their ^1H and ^{13}C nmr spectra.

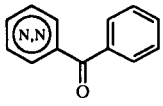
Scheme 1



1



3-8



2

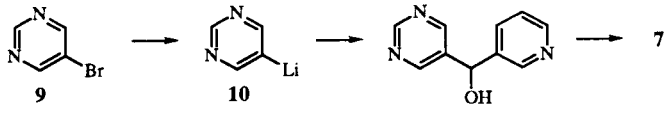
R	
3-pyridazinyl	**3**
4-pyridazinyl	**4**
2-pyrimidinyl	**5**
4-pyrimidinyl	**6**
5-pyrimidinyl	**7**
2-pyrazinyl	**8**

Results and Discussion.

The convenient availability of 5-lithiopyrimidine (**10**) [7] which is accessible from commercial 5-bromopyrimidine (**9**) by halogen-lithium exchange and its reported smooth reactivity towards various aldehydes [6,7] prompted us to prepare 3-pyridyl-5-pyrimidinylmethanone (**7**) by reaction of **10** with 3-pyridinecarbaldehyde and subsequent oxidation of the resulting alcohol **11** with activated manganese dioxide. The target ketone **7** was obtained in 57% overall yield (see Scheme 2).

The ketones **3-6** and **8** were synthesized employing a strategy previously reported for the preparation of pyridyl-3-pyridylmethanones: Reaction of 3-lithiopyridine (**13**) (prepared from 3-bromopyridine (**12**) *via* halogen-lithium exchange) with pyridinecarbonitriles or alkyl

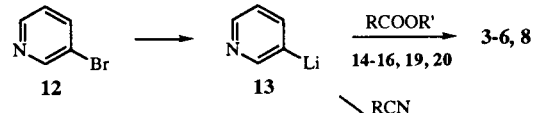
Scheme 2



9 **10** **11** **7**

pyridinecarboxylates [8-11] is known to give the corresponding dipyridyl ketones. Thus, the ketones **4**, **6**, and **8** could be obtained in high yields by quenching **13** with easily accessible ethyl 4-pyridazinecarboxylate (**14**) [12], methyl 4-pyrimidinecarboxylate (**15**) [13] or methyl 2-pyrazinecarboxylate (**16**) [14], respectively (see Scheme 3). The reported convenient syntheses of 3-cyanopyridazine (**17**) [15] and 2-cyanopyrimdine (**18**) [16] prompted us to attempt the syntheses of the ketones **3** and **5** starting from these intermediates. However, by quenching **13** with diazine carbonitriles **17** or **18**, respectively, we obtained the corresponding ketones **3** and **5** in only poor yields (<10%) due to predominant attack of **13** at the diazine systems. In contrast, ethyl 3-pyridazinecarboxylate (**19**) [17] as well as ethyl 2-pyrimidinylcarboxylate (**20**) [18] reacted smoothly with **13** to give ketones **3** and **5** in 57% and 46% yield, respectively (see Scheme 3).

Scheme 3



12 **13**

RCOOR' → **3-6, 8** (**14-16, 19, 20**)

RCN → **17, 18** → **3, 5** (< 10%)

R	R'	
3-pyridazinyl	Et	**19**
3-pyridazinyl	–	**17**
4-pyridazinyl	Et	**14**
2-pyrimidinyl	Et	**20**
2-pyrimidinyl	–	**18**
4-pyrimidinyl	Me	**15**
2-pyrazinyl	Me	**16**

The ^1H chemical shifts and coupling constants as well as ^{13}C chemical shifts of the ketones **3-8** are given in Tables 1 and 2. The ^{13}C signals could be assigned due to chemical shift considerations, resonance multiplicities (DEPT) [19] and by application of ^{13}C, ^1H correlation experiments (HETCOR) [20]. For the assignment of non-

Table 1

^{1}H NMR (deuteriochloroform) δ (ppm) and Coupling Constants (Hz) of Ketones **3-8**

No.	Diazine-H					3-Pyridyl-H			
	H-2	H-3	H-4	H-5	H-6	H-2 [a]	H-4 [b]	H-5 [c]	H-6 [d]
3	—	—	8.22 (dd, $J_{4,6}$ = 1.7, $J_{4,5}$ = 8.5)	7.72 (dd, $J_{5,6}$ = 5.0, $J_{4,5}$ = 8.5)	9.53 (dd, $J_{4,6}$ = 1.7, $J_{5,6}$ = 5.0)	9.38	8.54	7.43	8.80
4	—	9.39 (dd, $J_{3,6}$ = 1.4, $J_{3,5}$ = 2.4)	—	7.69 (dd, $J_{3,5}$ = 2.4, $J_{5,6}$ = 5.1)	9.40 (dd, $J_{3,6}$ = 1.4, $J_{5,6}$ =5.1)	8.92	8.07	7.45	8.81
5	—	—	8.95 (d, $J_{5,4/6}$ = 5.0)	7.50 (t, $J_{5,4/6}$ = 5.0)	8.95 (d, $J_{5,4/6}$ = 5.0)	9.27	8.39	7.42	8.79
6	9.34 (d, $J_{2,5}$ = 1.4)	—	—	7.93 (dd, $J_{2,5}$ = 1.4, $J_{5,6}$ = 5.0)	9.00 (d, $J_{5,6}$ = 5.0)	9.31	8.41	7.39	8.76
7	9.33 (s)	—	9.04 (s)	—	9.04 (s)	8.93	8.07	7.44	8.80
8	—	9.26 (d, $J_{3,6}$ = 1.3)	—	8.75 (d, $J_{5,6}$ = 2.6)	8.63 (dd, $J_{3,6}$ 1.3, $J_{5,6}$ = 2.6)	9.28	8.37	7.39	8.74

[a] dd, $J_{2,5}$ = 0.8-1.0, $J_{2,4}$ = 2.2-2.4. [b] ddd, $J_{4,6}$ = 1.8-1.9, $J_{2,4}$ = 2.2-2.4, $J_{4,5}$ = 7.9-8.1. [c] ddd, $J_{2,5}$ = 0.8-1.0, $J_{5,6}$ = 4.8-5.0, $J_{4,5}$ = 7.9-8.1. [d] dd, $J_{4,6}$ = 1.8-1.9, $J_{5,6}$ = 4.8-5.0.

Table 2

^{13}C NMR (deuteriochloroform) δ (ppm) of Ketones **3-8**

No.	Diazine-C					3-Pyridyl-C					C=O
	C-2	C-3	C-4	C-5	C-6	C-2	C-3	C-4	C-5	C-6	
3	—	157.0	127.3	127.5	152.8	152.2	131.1	138.6	123.1	153.5	190.5
4	—	149.0	133.0	124.9	151.8	150.7	130.7	136.9	123.7	154.3	191.7
5	161.3	—	157.5	122.7	157.5	152.2	131.0	138.0	123.2	153.5	189.7
6	158.1	—	159.7	120.0	159.1	152.0	130.5	138.0	123.1	153.6	190.7
7	161.2	—	157.6	130.1	157.6	150.7	131.5	136.8	123.7	154.1	191.0
8	148.6	146.0	—	147.3	142.8	151.9	131.2	137.9	123.1	153.3	190.6

protonated heteroaromatic carbon atoms in ketones **4** and **7**, we applied long-range INEPT experiments with selective DANTE excitation [21].

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. The ir spectra (potassium bromide) were recorded on a Shimadzu IR-470. Mass spectra were obtained on a Finnigan SSQ 7000 instrument (70 eV, electron impact). The nmr spectra were recorded in deuteriochloroform solutions on a Varian Gemini 200 spectrometer (200 MHz for ^{1}H, 50 MHz for ^{13}C). The singlet of the solvent signal (deuteriochloroform) was used as an internal standard, which was related to TMS with δ 7.24 ppm (^{1}H) and δ 77.0 ppm (^{13}C), respectively. The ^{1}H-nmr spectra were recorded with a digital resolution of 0.2 Hz/data point. The ^{13}C, ^{1}H shift correlation spectra were obtained using the standard Varian HETCOR [20] pulse sequence with an acquisition time of 0.17 seconds, an average $^1J_{CH}$ of 170 Hz, 256 increments with 32 transients per increment, a delay of 1.5 seconds between transients and data were processed as a 2048 x 512 matrix using sine-bell functions for weighting in both domains. Spectral widths of 0.5 kHz and 3 kHz were employed in the F_1 (^{1}H) and the F_2 (^{13}C) dimensions, respectively. Reactions were monitored by tlc using Polygram SIL G/UV$_{254}$ (Macherey-Nagel) plastic-packed plates (0.25 mm layer thickness) and visualized using an uv lamp or iodine vapour. Elemental analyses were carried out by Mikroanalytisches Laboratorium, Institute of Physical Chemistry, University of Vienna.

3-Pyridyl-5-pyrimidinylmethanone (**7**).

To a cooled solution (-110°) of 477 mg (3 mmoles) of 5-bromopyrimidine in 10 ml of a 1:1 mixture of dry THF and dry ether were added 2.1 ml (3.3 mmoles) of a 1.6 *M* solution of *n*-butyllithium in *n*-hexane under a nitrogen atmosphere while keeping the temperature below -100°. After 15 minutes, a solution of 353 mg (3.3 mmoles) of 3-pyridylcarbaldehyde in 3 ml of dry THF was added slowly. The mixture was allowed to warm up to room temperature within 2 hours. Then 10 ml of saturated aqueous ammonium chloride solution were added, the organic layer was separated and the aqueous phase was exhaustively extracted with methylene chloride. The combined organic layers were dried over anhydrous sodium sulfate and evaporated to dryness. The oily orange residue was dissolved in 10 ml of methylene chloride and 1.22 g (14 mmoles) of activated manganese dioxide were added slowly. The suspension was then stirred at room temperature. After 24 hours, the mixture was filtered through Celite, the Celite was washed several times with methylene chloride and the combined organic layers were evaporated to dryness to give crude **7**. Recrystallisation from diisopropyl ether-ethyl acetate gave 317 mg (57%) of **7** as yellowish needles, mp 129°; ir (potassium bromide): ν 1657 (C=O); ms: m/z (%) 185 (M^+, 44), 157 (21), 106 (36), 78 (63), 52 (43), 51 (100).

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.90; H, 3.90; N, 22.80.

General Procedure for the Preparation of Ketones **3-6** and **8**.

To a cooled solution (-90°) of 474 mg (3 mmoles) of 3-bromopyridine in 10 ml of a 1:1 mixture of dry ether and dry THF was added slowly 2.1 ml (3.3 mmoles) of a 1.6 *M* solution of *n*-butyllithium in *n*-hexane under a nitrogen atmosphere. After additional stirring of the resulting yellowish green suspension for 15 minutes at -90°, 3 mmoles of the appropriate alkyl diazine carboxylate (**14** [12], **15** [13], **16** [14], **19** [17] or **20** [18]) dissolved in 10 ml of a 1:1 mixture of dry ether and dry THF were added while keeping the temperature below -90°. Then the reaction mixture was allowed to warm up to room temperature within 12 hours. After addition of 10 ml of saturated aqueous ammonium chloride solution, the organic layer was separated and the aqueous phase was exhaustively extracted with methylene chloride. The combined organic layers were dried over anhydrous sodium sulfate and evaporated to dryness. The residue was purified by recrystallization to afford ketones **3-6** and **8**.

3-Pyridazinyl-3-pyridylmethanone (**3**).

Compound **3** was prepared starting from 456 mg (3 mmoles) of **19** [17]. Crude **1** was recrystallized from diisopropyl ether to afford 316 mg (57%) of **3** as orange crystals, mp 73°; ir (potassium bromide): ν 1666 (C=O); ms: m/z (%) 185 (M^+, 45), 184 (20), 157 (50), 106 (25), 78 (100), 51 (81).

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.72; H, 3.80; N, 22.53.

4-Pyridazinyl-3-pyridylmethanone (**4**).

Compound **4** was prepared starting from 456 mg (3 mmoles) of **14** [12]. Crude **4** was recrystallized from diisopropyl ether-ethyl acteate to afford 260 mg (47%) of **4** as yellow crystals, mp 87°; ir (potassium bromide): ν 1658 (C=O); ms: m/z (%) 185 (M^+, 100), 106 (80), 78 (94), 51 (82).

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.71; H, 3.77; N, 22.49.

3-Pyridyl-2-pyrimidinylmethanone (**5**).

Compound **5** was prepared starting from 456 mg (3 mmoles) of **20** [18]. Crude **5** was recrystallized from diisopropyl ether to afford 255 mg (46%) of **5** as yellow crystals, mp 96°; ir (potassium bromide): ν 1680 (C=O); ms: m/z (%) 185 (M^+, 100), 106 (18), 78 (57), 51 (38).

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.57; H, 3.77; N, 22.36.

3-Pyridyl-4-pyrimidinylmethanone (**6**).

Compound **6** was prepared starting from 414 mg (3 mmoles) of **15** [13]. Crude **6** was recrystallized from diisopropyl ether to afford 405 mg (73%) of **6** as yellow crystals, mp 70°; ir (potassium bromide): ν 1676 (C=O); ms: m/z (%) 185 (M^+, 100), 157 (36), 106 (42), 78 (64), 57 (45), 56 (26), 52 (26), 51 (60).

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.68; H, 3.85; N, 22.31.

2-Pyrazinyl-3-pyridylmethanone (**8**).

Compound **8** was prepared starting from 414 mg (3 mmoles) of **16** [14]. Crude **8** was recrystallized from diisopropyl ether to afford 383 mg (69%) of **6** as orange crystals, mp 72°; ir (potassium bromide): ν 1670 (C=O); ms: mlz (%) 185 (M^+, 100), 157 (20), 106 (30), 78 (58), 52 (22), 51 (56).

Anal. Calcd. for $C_{10}H_7N_3O$: C, 64.86; H, 3.81; N, 22.69. Found: C, 64.60; H, 4.00; N, 22.36.

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