Pyrazoles. 6 [1].
Synthesis of Novel Heteroaryl 4-Pyrazolyl Ketones

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The preparation of a variety of novel heteroaromatic analogues of benzophenone **2-11** characterized by a 4-pyrazolyl moiety and a thienyl-, azinyl- or diazinyl-system starting from 1,4-dilithiopyrazole is reported.

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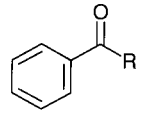
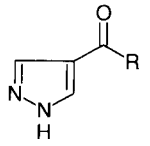
Benzophenone represents an important building block for the construction of a wide variety of bio-active compounds. Within a project directed towards isosteric modification of drug molecules (replacement of carbocyclic aromatic systems by heteroarenes) we have previously elaborated convenient methods for the synthesis of heteroaromatic benzophenone analogues of type **1** [4-10]. In continuation of these efforts we now became interested in heteroaryl 4-pyrazolyl ketones of type **2-11** in which R is represented by either a thiophene system or a pyridine-, pyrazine-, pyrimidine-, or pyridazine-ring. The latter type of compounds, in which there is an influence on the electron-distribution of the methane carbon atom by both a π-excessive and a π-deficient heteroaromatic system, appears to be of particular interest for bio-isosterism studies.

Scheme 1



1

R = 3-pyridazinyl
4-pyridazinyl
2-pyrazinyl
4-pyrimidinyl
4-pyrazolyl



2-11

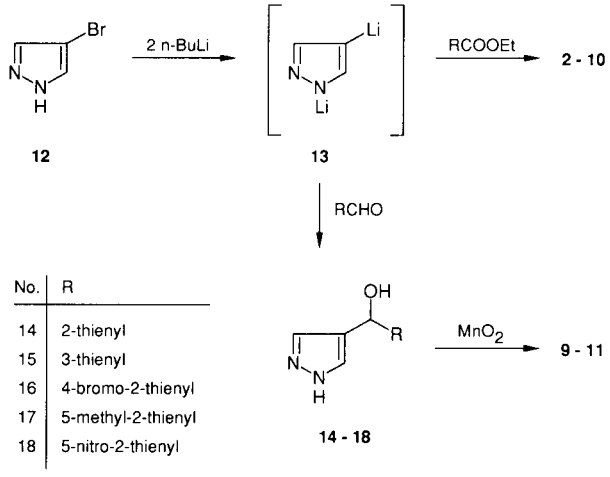
No.	R
2	2-pyridinyl
3	3-pyridinyl
4	4-pyridinyl
5	3-pyridazinyl
6	4-pyridazinyl
7	4-pyrimidinyl
8	2-pyrazinyl
9	2-thienyl
10	3-thienyl
11	4-bromo-2-thienyl

The convenient availability of 1,4-dilithiopyrazole (**13**) [11,8] together with its recently reported smooth transformation into 4-benzoylpyrazole upon reaction with ethyl benzoate [8] now prompted us to react **13** with alkyl carboxylates derived from the above mentioned heteroaromatic systems. Employing azine- and diazinecarboxylic acid esters we obtained the target ketones **2-8**, albeit in only modest yields. Similarly, we succeeded in the preparation of the 4-pyrazolyl thienyl ketones **9** and **10** by reaction of **13** with the corresponding thiophene carboxylates. In all these cases formation of tertiary alcohols could be avoided simply by addition of the dilithio-species **13** to the electrophile.

Employment of thiophenecarbaldehydes as reactants provided access to the novel benzhydrol analogues **14-18**. Subsequent manganese dioxide oxidation of compounds **14-16** gave the ketones **9-11**. This approach, however, does not permit enhancement of the yields of the target ketones, since we encountered difficulties in attempts to extract them quantitatively from the inorganic material.

For analytical and spectroscopic data of the compounds prepared see Tables 1 and 2.

Scheme 2



No.	R
14	2-thienyl
15	3-thienyl
16	4-bromo-2-thienyl
17	5-methyl-2-thienyl
18	5-nitro-2-thienyl

Thus, by employing 1,4-dilithiopyrazole (**13**) as the key intermediate, short syntheses for a variety of heteroaryl 4-pyrazolyl ketones could be elaborated. With respect to the modest yields obtained in the C-C bond formation step, it should be emphasized that only easily accessible or even commercially available compounds are required as starting materials.

Table 1
Physical and Analytical Data of Compounds 2-11, 14-18

Compound No.	Mp (°C) Recrystallization Solvent [a]	Molecular Formula (MW)	Elemental Analysis (Calcd.%/Found%) C	H	N
2	113-116	$C_9H_7N_3O$	62.42	4.07	24.27
	A	(173.18)	62.16	4.37	24.19
3	183-185	$C_9H_7N_3O$	62.42	4.07	24.27
	-	(173.18)	62.37	4.17	24.17
4	207-209	$C_9H_7N_3O$	62.42	4.07	24.27
	B	(173.18)	62.57	4.07	24.02
5	214-215	$C_8H_6N_4O$	55.17	3.47	32.17
	-	(174.16)	55.10	3.52	32.45
6	187-190	$C_8H_6N_4O$ [b]	55.13	3.87	29.90 [f,g]
	A	(174.16)	55.32	3.78	29.73
7	151	$C_8H_6N_4O$ [c]	55.14	3.75	30.62 [f,h]
	A	(174.16)	55.21	3.85	30.81
8	179-181	$C_8H_6N_4O$ [d]	55.14	3.75	30.62 [f,h]
	A	(174.16)	55.06	3.38	30.82
9	165-167	$C_8H_6N_2OS$	53.92	3.39	15.72
	A	(178.21)	54.21	3.57	15.53
10	127-130	$C_8H_6N_2OS$	53.92	3.39	15.72
	A	(178.21)	53.68	3.66	15.51
11	171-174	$C_8H_5BrN_2OS$	37.37	1.96	10.90
	A	(257.11)	37.62	2.06	10.76
14	125-127	$C_8H_8N_2OS$	53.32	4.47	15.54
	B	(180.22)	53.35	4.57	15.31
15	140-141	$C_8H_8N_2OS$	53.32	4.47	15.54
	B	(180.22)	53.33	4.57	15.46
16	110-112	$C_8H_7BrN_2OS$	37.08	2.72	10.81
	-	(259.12)	37.00	2.67	10.66
17	115-120	$C_9H_{10}N_2OS$	55.65	5.19	14.42
	A	(194.25)	55.73	5.10	14.28
18	160	$C_8H_7N_3O_3S$ [e]	42.66	3.13	18.66
	B	(225.22)	42.84	2.91	18.65

[a] A: Diisopropyl ether-ethyl acetate B: ethyl acetate. [b] High-resolution mass spectrum for M^+: Calcd. m/z = 174.0542. Found: m/z = 174.0546 ± 0.0008. [c] High-resolution mass spectrum for M^+: Calcd. m/z = 174.0542. Found: m/z = 174.0543 ± 0.0008. [d] High-resolution mass spectrum for M^+: Calcd. m/z = 174.0542. Found: m/z = 174.0545 ± 0.0008. [e] High-resolution mass spectrum for M^+: Calcd. m/z = 225.0208. Found: m/z = 225.0211 ± 0.0008. [f] Elemental analyses of compounds 6-8 indicated co-crystallisation with 0.10-0.15 equivalents of ethyl acetate which could not be removed even on prolonged vacuum drying at 80°. However, the spectroscopic data together with high-resolution mass determination of M^+ provide an unequivocal proof for the assigned structures of these compounds. [g] Calcd. for $C_8H_6N_4O \cdot 0.15$ ethyl acetate. [h] Calcd. for $C_8H_6N_4O \cdot 0.1$ ethyl acetate.

EXPERIMENTAL

Melting points were determined on a Reichert-Kofler hot-stage microscope and are uncorrected. The ir spectra were recorded for potassium bromide pellets on a Jasco IRA-1 spectrophotometer. Mass spectra were obtained on the following instruments: Varian MAT 311A; Hewlett-Packard 5890A/5970B-MSD (glc/ms); Finnigan MAT 8230 (hrms), all EI/70 eV. The nmr spectra were recorded in deuteriodimethyl sulfoxide solutions on a Bruker AC 80 spectrometer (80.13 MHz for ^1H, 20.15 MHz for ^{13}C). Chemical shifts are given in δ-units downfield from tetramethylsilane. Assignments of ^{13}C chemical shifts are based on multiplicity selection applying the J-modulated spin-echo technique [12], on coupling information obtained from the ^1H-coupled ^{13}C-spectra ("gated decoupling") and on comparison with literature data [8,13]. Column chromatographic separations were performed on Merck Kieselgel 60 (70-230 mesh). All reactions with organolithium reagents were carried out under dry argon. Tetrahydrofuran was dried by passing through a column of aluminia (activity I, basic).

General Procedure for the Preparation of Heteroaryl 4-Pyrazolyl Ketones **2-10** *via* Reaction of 1,4-Dilithiopyrazole (**13**) with Alkyl Heteroarylcarboxylates.

To a solution of 1.47 g (10 mmoles) of 4-bromopyrazole (**12**) [14] in 20 ml of dry tetrahydrofuran 15 ml (24 mmoles) of a 1.6 *M*-solution of *n*-butyllithium in hexane was added dropwise at -70°, then the mixture was allowed to reach ambient temperature within 45 minutes. After stirring for additional 1.5 hours, the mixture was re-cooled to -70° and dropwise added to a cold (-70°), stirred, solution of 10 mmoles of the appropriate alkyl carboxylate (**2**, ethyl 2-pyridinecarboxylate; **3**, ethyl 3-pyridinecarboxylate; **4**, ethyl 4-pyridinecarboxylate; **5**, ethyl 3-pyridazinecarboxylate [15]; **6**, ethyl 4-pyridazinecarboxylate [16]; **7**, ethyl 4-pyrimidinecarboxylate [17]; **8**, ethyl 2-pyrazinecarboxylate [18]; **9**, ethyl 2-thiophenecarboxylate; **10**, methyl 3-thiophenecarboxylate [19]) in 20 ml of dry tetrahydrofuran. After the addition was

Table 2

Spectroscopic Data of Compounds 2-11, 14-18

Compound No.	IR (KBr) cm^{-1} [a]	MS (EI, 70 eV) m/z (% base peak)	^{1}H-NMR (deuteriodimethyl sulfoxide): δ (ppm) NH [b,c]	pyrazole H-3,5 [d]	other H
2	1650 (C=O)	173 (73), 172 (22), 145 (52), 95 (100)	13.46	8.52	pyridine-H: 8.76 (6), 8.04 (3,5), 7.67 (4)
3	1630 (C=O)	173 (72), 95 (100), 81 (13), 51 (22)	13.60	8.24	pyridine-H: 8.96 (2), 8.79 (6), 8.13 (4), 7.56 (5)
4	1650 (C=O)	173 (49), 145 (15), 95 (100), 51 (22)	13.60	8.24	pyridine-H: 8.78 (2,6), 7.68 (3,5)
5	1635 (C=O)	174 (35), 95 (100), 53 (15), 52 (15)	13.50	8.53	pyridazine-H: 9.45 (6), 8.19 (4), 7.94 (5) $J_{4,5}$ = 8.5 Hz, $J_{4,6}$ = 1.8 Hz, $J_{5,6}$ = 4.9 Hz
6	1645 (C=O)	174 (31), 149 (21), 95 (100)	13.60	8.32	pyridazine-H: 9.47 (3,6), 7.98 (5)
7	1655 (C=O)	174 (14), 95 (100)	13.60	8.75 [b] 8.35 [b]	pyrimidine-H: 9.42 (2), 9.10 (6), 7.97 (5) $J_{2,5}$ = 1.4 Hz, $J_{2,6}$ = 0 Hz, $J_{5,6}$ = 5.0 Hz
8	1625 (C=O)	174 (27), 95 (100)	13.60	8.60 [b] 8.40 [b]	pyrazine-H: 9.17 (3), 8.89 (6), 8.82 (5) $J_{3,5}$ = 1.4 Hz, $J_{3,6}$ = 0 Hz, $J_{5,6}$ = 2.5 Hz
9	1620 (C=O)	178 (64), 111 (21), 95 (100), 84 (31)	13.60	8.33	thiophene-H: 8.00 (3,5), 7.26 (4) $J_{3,4}$ = 4.2 Hz, $J_{3,5}$ = 0 Hz, $J_{4,5}$ = 4.5 Hz
10	1655 (C=O)	178 (47), 111 (21), 95 (100)	13.50	8.25	thiophene-H: 8.41 (2), 7.66 (5), 7.53 (4), $J_{2,4}$ = 1.3 Hz, $J_{2,5}$ = 2.7 Hz, $J_{4,5}$ = 5.0 Hz
11	1605 (C=O)	256/258 (23), 95 (100)	13.60	8.39	thiophene-H: 8.12 (5), 8.00 (3) $J_{3,5}$ = 1.3 Hz
14	-	180 (25), 163 (26), 95 (100), 85 (51), 84 (37)	12.60	7.47	thiophene-H: 7.36 (5), 6.98-6.88 (3,4), $J_{3,4}$ = 3.4 Hz, $J_{3,5}$ = 1.9 Hz, $J_{4,5}$ = 4.5 Hz; 5.91 (C*H*OH) [e], 5.87 (OH) [c], J_{CHOH} = 5.2 Hz
15	-	180 (31), 163 (24), 95 (100), 85 (41), 84 (26), 69 (19)	12.60	7.41	thiophene-H: 7.42 (5), 7.24 (2), 7.03 (4), $J_{2,4}$ = 1.3 Hz, $J_{2,5}$ = 2.8 Hz, $J_{4,5}$ = 4.9 Hz; 5.72 (C*H*OH) [e], 5.50 (OH) [c], J_{CHOH} = 5.0 Hz
16	-	258/260 (12), 179 (23), 95 (100)	12.70	7.51	thiophene-H: 7.50 (5), 6.87 (3), $J_{3,5}$ = 1.5 Hz; 6.06 (OH) [c], 5.92 (C*H*OH) [e], J_{CHOH} = 5.0 Hz
17	-	194 (25), 177 (38), 99 (100), 95 (58)	12.60	7.46	thiophene-H: 6.68-6.55 (3,4), $J_{3,4}$ = 3.6 Hz; 5.81 (C*H*OH) [e], 5.75 (OH) [c], J_{CHOH} = 4.9 Hz; 2.37 (CH_3)
18	-	225 (14), 179 (73), 111 (28), 95 (100)	12.70	7.57	thiophene-H: 7.97 (4), 6.96 (3), $J_{3,4}$ = 4.4 Hz; 6.46 (OH) [c], 5.98 (C*H*OH) [e], J_{CHOH} = 4.9 Hz

[a] The ir spectra of compounds **2-11**, **14-18** exhibit broad absorption bands between 2900 and 3300 cm^{-1} due to N-H (**2-11**) or N-H/O-H (**14-18**) stretching vibrations. [b] Broad signal. [c] Exchangeable with deuterium oxide. [d] Due to rapid proton exchange between pyrazole-N-1 and N-2 the signals of pyrazole H-3 and pyrazole H-5 appear as one two-proton singlet. [e] Singlet after addition of deuterium oxide.

complete, the cooling bath was removed, the reaction mixture was allowed to regain room temperature and stirring was continued for additional 1.5 hours. Saturated ammonium chloride solution (20 ml) was added, the mixture was stirred for 15 minutes and was then diluted with diethyl ether. The organic layer was separated and the aqueous phase was extracted with two 200 ml-portions of diethyl ether. The combined organic layers were washed with water, dried, and evaporated. The residue was purified either by column chromatography and/or recrystallisation to afford the ketones **2-11**.

4-Pyrazolyl 2-Pyridinyl Ketone (**2**).

Column chromatography (dichloromethane-ethyl acetate, 1:3) followed by recrystallisation from diisopropyl ether-ethyl acetate afforded 416 mg (24%) of pale yellow crystals.

4-Pyrazolyl 3-Pyridinyl Ketone (**3**).

After multiple digestion of the crude product with cold diisopropyl ether 365 mg (21%) of pale yellow crystals were obtained.

4-Pyrazolyl 4-Pyridinyl Ketone (**4**).

Recrystallisation from ethyl acetate afforded 710 mg (41%) of colorless crystals.

4-Pyrazolyl 3-Pyridazinyl Ketone (**5**).

Multiple digestion with cold diisopropyl ether gave 418 mg (24%) of pale yellow crystals.

4-Pyrazolyl 4-Pyridazinyl Ketone (**6**).

Column chromatography (dichloromethane-ethyl acetate, 1:3) followed by recrystallisation from diisopropyl ether-ethyl acetate afforded 175 mg (10%) of pale yellow crystals.

4-Pyrazolyl 4-Pyrimidinyl Ketone (**7**).

Recrystallisation from diisopropyl ether-ethyl acetate gave 400 mg (23%) of pale yellow crystals.

2-Pyrazinyl 4-Pyrazolyl Ketone (**8**).

Recrystallisation from diisopropyl ether-ethyl acetate gave 522 mg (30%) of yellow crystals.

4-Pyrazolyl 2-Thienyl Ketone (**9**).

Column chromatography (dichloromethane-ethyl acetate, 1:3) followed by recrystallisation from diisopropyl ether-ethyl acetate gave 250 mg (14%) of colorless crystals.

4-Pyrazolyl 3-Thienyl Ketone (**10**).

Column chromatography (dichloromethane-ethyl acetate, 1:3) followed by recrystallisation from diisopropyl ether-ethyl acetate gave 267 mg (15%) of colorless crystals.

General Procedure for the Preparation of Heteroaryl 4-Pyrazolylmethanols **14-18** *via* Reaction of 1,4-Dilithiopyrazole (**13**) with Heteroarylcarbaldehydes.

To a solution of 1,4-dilithiopyrazole (**13**) prepared from 1.47 g (10 mmoles) of 4-bromopyrazole (**12**) (as described above for the preparation of ketones **2-10**) a solution of 11 mmoles of the appropriate carbaldehyde in 5 ml of dry tetrahydrofuran was added dropwise at -70°. After the addition was complete, the cooling bath was removed. The mixture was allowed to reach ambient temperature within 1.5 hours and was stirred for one additional hour. Saturated ammonium chloride solution (30 ml) was added and the mixture was extracted with three 20 ml-portions of diethyl ether. The combined organic layers were washed with water, dried, and evaporated *in vacuo*. The residue was recrystallized or digested to afford the carbinols **14-18**.

4-Pyrazolyl-2-thienylmethanol (**14**).

Recrystallisation from ethyl acetate afforded 650 mg (36%) of colorless crystals; ^{13}C-nmr (deuteriodimethyl sulfoxide): [20] δ 158.78 (th C-2), 126.47 (th C-4), 125.10 (pyrazole C-4), 124.47 (th C-5), 123.59 (th C-3), 63.72 (CHOH).

4-Pyrazolyl-3-thienylmethanol (**15**).

Recrystallisation from ethyl acetate afforded 667 mg (37%) of colorless crystals; ^{13}C-nmr (deuteriodimethyl sulfoxide): [20] δ 147.59 (th C-3), 126.81 (th C-4), 125.87 (th C-5), 125.24 (pyrazole C-4), 120.41 (th C-2), 63.98 (CHOH).

(4-Bromo-2-thienyl)-4-pyrazolylmethanol (**16**).

Digestion with cold diisopropyl ether gave 1.115 g (43%) of colorless crystals; ^{13}C-nmr (deuteriodimethyl sulfoxide): [20] δ 152.71 (th C-2), 135-125 (very broad, pyrazole C-3,5), 125.64 (th C-3), 124.22 (pyrazole C-4), 122.08 (th C-5), 107.71 (th C-4), 63.30 (CHOH).

(5-Methyl-2-thienyl)-4-pyrazolylmethanol (**17**).

Recrystallisation from ethyl acetate-diisopropyl ether (9:1) afforded 758 mg (39%) of colorless crystals; ^{13}C-nmr (deuteriodimethyl sulfoxide): [20] δ 148.16 (th C-2), 137.80 (th C-5), 125.00 (pyrazole C-4), 124.36 (th C-4), 123.29 (th C-3), 63.73 (CHOH), 14.96 (CH_3).

(5-Nitro-2-thienyl)-4-pyrazolylmethanol (**18**).

Recrystallisation from ethyl acetate followed by multiple digestion with cold diisopropyl ether gave 180 mg (8%) of brown crystals.

General Procedure for the Preparation of Ketones **9-11** by Oxidation of Alcohols **14-16**.

To a stirred suspension of the alcohol (1 mmole) in 10 ml of dichloromethane tetrahydrofuran was added until a clear solution was obtained (1-10 ml). Then 1.30 g (15 mmoles) of activated manganese dioxide [21] were added and the mixture was stirred for 20 hours. After filtration, the brown residue was washed several times with ethyl acetate. The combined filtrates were evaporated *in vacuo* and the residue was recrystallized from diisopropyl ether-ethyl acetate. Thus, the following compounds were obtained.

Ketone **9**.

Oxidation of **14** (180 mg, 1 mmole) gave 84 mg (47%) of **9**.

Ketone **10**.

Oxidation of **15** (180 mg, 1 mmole) gave 55 mg (31%) of **10**.

(4-Bromo-2-thienyl) 4-Pyrazolyl Ketone (**11**).

Oxidation of **16** (259 mg, 1 mmole) gave 147 mg (57%) of light brown crystals; ^{13}C-nmr (deuteriodimethyl sulfoxide): [20] δ 177.96 (C=O), 144.75 (th C-2), 133.65 (th C-3), 131.44 (th C-5), 120.02 (pyrazole C-4), 109.93 (th C-4).

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[20] In the ^{13}C-nmr spectra of NH-pyrazoles **11**, **14**, **15**, **16**, and **17** the signals due to pyrazole C-3 and pyrazole C-5 either appear as one very broad signal between 125 and 135 ppm or they cannot be detected at all. This phenomenon can be explained on basis of a dynamic behaviour (proton exchange between pyrazole N-1 and N-2) with a rate in the range of the nmr-timescale.

[21] Active manganese dioxide (prepared according to ref [22]) was heated *in vacuo* to 130-140° for 3 hours before use.

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