*N*1-Substituted 3,5-Dimethoxy-4-halogeno-1*H*-pyrazoles: Synthesis and NMR Study

Wolfgang Holzer* and Heidi Gruber [1]

Institute of Pharmaceutical Chemistry, University of Vienna, Pharmaziezentrum, Althanstraße 14, A-1090 Vienna, Austria

Received April 10, 1995

The synthesis of 1-methyl- and 1-benzyl-3,5-dimethoxy-4-halogeno-1*H*-pyrazoles is described. Moreover, detailed nmr spectroscopic studies with the title compounds are presented. The highly shielded pyrazole C-4 atom in the corresponding 4-iodo congeners was found to have a ^{13}C-chemical shift of only ~27 ppm.

J. Heterocyclic Chem., **32**, 1351 (1995).

Whereas *N*-substituted 3,5-dihydroxypyrazoles are considered to occur as 3-hydroxy-2-pyrazolin-5-ones [2], with their 3,5-dimethoxy analogues the aromatic pyrazole nucleus is "fixed". The latter compounds seem interesting as they are characterized by a highly activated 4-position on the pyrazole moiety. However, the reactivity of such compounds in simple electrophilic reactions has not been studied so far. Thus, we here report on halogenation reactions with 1-methyl- and 1-benzyl-3,5-dimethoxypyrazole leading to the corresponding 4-halogeno derivatives, which can act as educts for further functionalizations. Additionally, we present detailed nmr spectroscopic studies (^{1}H- and ^{13}C-nmr) with the title compound, which were found to be also interesting from the spectroscopic point of view.

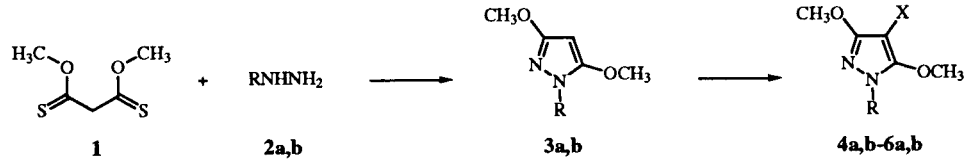
Synthesis.

The educt **3a** was prepared according to a known procedure [3] by reaction of dimethyl dithiomalonate (**1**) [4] with methylhydrazine (**2a**) [5]. Similarly, 1-benzyl-3,5-dimethoxypyrazole (**3b**) could be obtained from **1** and benzylhydrazine dihydrochloride (**2b**•2HCl). Iodination of compounds **3** to the 4-iodopyrazoles **6a** and **6b** was smoothly achieved by reaction with iodine/potassium iodide in water according to the method of Hüttel [6]. Treatment of **3a** with bromine in dichloromethane at 0° afforded the 4-bromo product **5a** in good yield, analogously **5b** was obtained from bromination of **3b**. Reaction of **3a** with sulfuryl chloride did not result in the formation of the expected 4-chloro derivative **4a**, instead 4,4-dichloro-2,4-dihydro-3-methoxy-2-methylpyrazol-3-one (**7**) was isolated from the reaction mixture. The formation of the latter product can be explained in terms of ether cleavage of the 5-methoxy group in **3a**, tautomerization of the resulting 5-hydroxypyrazole to the corresponding pyrazol-3-one and subsequent chlorination of the activated methylene group in 4-position of the pyrazolone system. However, treatment of **3a** or **3b** with *N*-chlorosuccinimide in tetrachloromethane afforded the 4-chloro-3,5-dimethoxypyrazoles **4a** and **4b** in acceptable yields.

NMR Spectroscopic Investigations.

The ^{1}H-nmr data of compounds **3-6** are given in the Experimental, ^{13}C-nmr data are collected in Table 1. Unambiguous assignment for all resonances was carried out as follows: long-range INEPT experiments with selective excitation (DANTE) [7] of the NCH_3 (NCH_2) protons allowed us to identify the pyrazole C-5 resonance *via* the $^3J(C5,NCH_{3(2)})$ coupling. The distinction between pyrazole C-5 and pyrazole C-3 is also independently possible from the fully ^{1}H-coupled ^{13}C-nmr spectrum considering the fact that the pyrazole C-5 signal has a more complicated splitting pattern than that of pyrazole C-3 due to the additional coupling with the $NCH_{3(2)}$ protons. Distinction between the 3-OCH_3 and 5-OCH_3 resonances in the ^{1}H-nmr spectra was achieved employing further long-range INEPT experiments: selective excitation of 5-OCH_3 enhances the signal of pyrazole C-5 (identified as described above), and *vice versa* the pyrazole C-3 resonance emerges upon excitation of 3-OCH_3). Finally, selective 1D-HETCOR experiments [8] exciting the thus identified methoxy protons

Scheme 1



1 **2a,b** **3a,b** **4a,b-6a,b**

2-6: **a**: R = Me, **b**: R = CH_2Ph **4**: X = Cl, **5**: X = Br, **6**: X = I

Table 1

^{13}C-Chemical Shifts (δ, ppm) and Selected ^{13}C,^{1}H Spin Coupling Constants (Hz) of Pyrazoles **3-6** (in Deuteriochloroform Solution)

	Chemical Shifts							Coupling Constants				
	Pyrazole-C			Other C								
No.	C-3	C-4	C-5	3-OMe	5-OMe	$NCH_{3(2)}$	Other C	$^{1}J(3\text{-}OCH_3)$	$^{1}J(5\text{-}OCH_3)$	$^{1}J(NCH_{3(2)})$	$^{3}J(C3,OCH_3)$	Other Couplings Determined
3a	161.2	70.3	155.3	55.2	58.3	32.8	—	144.9	145.8	139.6	4.0	$^{3}J(C5,NCH_3)$ = 2.4, $^{1}J(C4,H4)$ = 179.0
3b	161.4	70.8	155.3	55.3	58.4	49.7	[a]	144.9	145.9	139.0	4.0	$^{3}J(C5,NCH_2)$ = 2.6, $^{1}J(C4,H4)$ = 178.8, $^{3}J(C5,OCH_3)$ = 4.8
4a	156.6	78.3	149.4	55.5	60.3	33.9	—	145.9	146.9	140.3	3.8	
4b	156.8	79.1	149.4	55.5	60.4	50.9	[b]	145.9	147.0	139.7	3.8	$^{3}J(C5,NCH_2)$ = 2.7, $^{3}J(C5,OCH_3)$ = 4.1
5a	157.7	62.4	150.8	55.5	60.8	33.9	—	145.8	146.8	140.3	3.9	
5b	157.9	63.2	150.9	55.6	60.9	51.0	[c]	145.9	147.0	139.7	3.9	
6a	160.3	26.6	153.7	55.5	61.5	34.0	—	145.7	146.7	140.3	3.9	
6b	160.5	27.6	153.8	55.6	61.6	51.1	[d]	145.8	146.8	139.6	3.8	

[a] Ph-C: 137.5 (1), 128.3 (3,5), 127.1 (4), 127.0 (2,6). [b] Ph-C: 137.0 (1), 128.5 (3,5), 127.6 (4), 127.1 (2,6). [c] Ph-C: 137.0 (1), 128.6 (3,5), 127.6 (4), 127.1 (2,6). [d] Ph-C: 137.1 (1), 128.6 (3,5), 127.6 (4), 127.1 (2,6).

enabled us to assign the corresponding signals of the directly attached OCH_3 carbons. Unambiguous determination of $^{3}J(C5,OCH_3)$ and $^{3}J(C5,NCH_{3(2)})$ for compounds **3a**, **3b** and **4b** was carried out *via* 2D long-range INEPT experiments [9] with selective excitation of the 5-OCH_3 and/or the N-$CH_{3(2)}$ proton transitions. The above techniques were also used to assign all resonances in the ^{1}H- and ^{13}C-nmr spectra of the 4,4-dichloro-3-pyrazolone **7**.

The chemical shift of 4.95 ppm (**3a**) and 5.05 ppm (**3b**), respectively, for the "aromatic" pyrazole H-4 proton in the parent compounds **3a,b** reflects the high electron density in 4-position of the pyrazole moiety. This is also confirmed by the corresponding ^{13}C-chemical shifts for pyrazole C-4 (**3a**: 70.3 ppm, **3b**: 70.8 ppm). Attachment of a chlorine atom in 4-position of the pyrazole system (**3a,b** → **4a,b**) results in a ~ 8 ppm downfield shift for the pyrazole C-4 signal, whereas pyrazole C-3 and pyrazole C-5 are markedly more shielded. Upfield shifts for C-3 and C-5 (compared to those of "parent compounds" **3a,b**) are also observed upon switching to 4-bromo (**5a,b**) and 4-iodo congeners (**6a,b**). The latter compounds are particularly interesting due to their extremely shielded pyrazole C-4 atoms (**6a**: δ (C-4) 26.6 ppm, **6b**: δ (C-4) 27.6 ppm). A search in the CSEARCH data base [10,11] including ~ 97000 ^{13}C-nmr spectra revealed no signals of "aromatic" carbons with comparably small chemical shifts, only that of pyrazole C-4 in 3,5-diamino-4-iodopyrazole (δ 29.53 ppm [12]) comes close. Thus, the pyrazole C-4 signal in **6a** is obviously the most shielded pyrazole-C atom ever observed (compare ref [13]) and it probably can be also considered as (one of) the most shielded aromatic carbon atoms at all.

EXPERIMENTAL

The ir spectra were recorded on a Perkin Elmer FTIR 1605 spectrometer. Mass spectra (glc/ms analyses) were obtained on a Hewlett Packard 5890A/5970B-MSD instrument (EI, 70 eV), the high-resolution mass spectra were carried out on a Finnigan MAT 8230 instrument. The nmr spectra were recorded on a Varian Unity*Plus* 300 spectrometer (299.95 MHz for ^{1}H, 75.43 MHz for ^{13}C) from deuteriochloroform solutions at 28°. The center of the solvent signal was used as an internal standard which was related to tetramethylsilane with δ 7.26 ppm (^{1}H) and δ 77.0 ppm (^{13}C). The ^{13}C-nmr spectra were recorded with digital resolutions of 0.55 Hz/data point (broad-band decoupled) and 0.29 Hz/data point (fully ^{1}H-coupled), ^{1}H-nmr spectra have a digital resolution of 0.25 Hz/data point. Chromatographic separations were carried out using preparative layer chromatography (plc plates Kieselgel 60 F-254, 2 mm layer thickness, Merck; extraction of the adsorbed material with ethyl acetate).

3,5-Dimethoxy-1-methyl-1*H*-pyrazole (**3a**).

Compound **3a** was prepared according to ref [3]; ^{1}H-nmr (deuteriochloroform): δ 4.95 (s, 1H, pyrazole H-4), 3.80 (s, 3H, C3-OCH_3), 3.79 (s, 3H, C5-OCH_3), 3.45 (s, 3H, NCH_3); ms: m/z (%) 142 (M^+, 72), 141 (36), 127 (46), 113 (16), 99 (12), 85 (100), 69 (67), 56 (11), 53 (11).

1-Benzyl-3,5-dimethoxy-1*H*-pyrazole (**3b**).

A stirred suspension of benzylhydrazine dihydrochloride (3.902 g, 20 mmoles) in 225 ml of diethyl ether was treated with 3.360 g (40 mmoles) of sodium bicarbonate and a few drops of water. After the evolution of carbon dioxide had ceased the resulting mixture was added dropwise to a stirred solution of **1** [4] (3.285 g, 20 mmoles) in 90 ml of ether and stirring was continued for 24 hours at room temperature. Then 250 ml of water were added, the etheral phase was separated and the remaining water phase was extracted with two 70 ml portions of ether. The combined ether phases were successively washed with 1*N* aqueous sodium hydroxide and water, dried over anhydrous sodium

sulfate and evaporated under reduced pressure. Vacuum-distillation of the residue afforded 2.706 g (62%) of a nearly colorless oil of bp 103°/0.4 mbar; ^{1}H-nmr (deuteriochloroform): δ 7.35-7.17 (m, 5H, Ph-H), 5.05 (s, 1H, pyrazole H-4), 5.02 (s, 2H, NCH_2), 3.85 (s, 3H, C3-OCH_3), 3.81 (s, 3H, C5-OCH_3); ms: m/z (%) 218 (M^+, 40), 217 (29), 187 (23), 91 (100), 69 (21), 65 (18).

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47; N, 12.84. Found: C, 65.85; H, 6.20; N, 12.87.

4-Chloro-3,5-dimethoxy-1-methyl-1*H*-pyrazole (**4a**).

A mixture of 142 mg (1 mmole) of **3a**, 134 mg (1 mmole) of *N*-chlorosuccinimide and 5 mg of dibenzoyl peroxide in 2 ml of tetrachloromethane was refluxed for 1 hour. After cooling, the reaction mixture was filtered, the filtrate was evaporated *in vacuo* and the residue was subjected to preparative layer chromatography (eluent: dichloromethane) to give 65 mg (37%) of a slightly yellowish oil; ^{1}H-nmr (deuteriochloroform): δ 4.08 (s, 3H, C5-OCH_3), 3.89 (s, 3H, C3-OCH_3), 3.50 (s, 3H, NCH_3); ms: m/z (%) 176/178 (M^+, 100/34), 177 (18), 175 (36), 161/163 (92/28), 147 (11), 133/135 (43/15), 119/121 (62/20), 103/105 (33/13), 90 (13), 83 (24), 75 (12), 47 (10); high-resolution ms: Calcd. for $C_6H_9ClN_2O_2$: 176.0353. Found: 176.0355 ± 0.0017, [14].

1-Benzyl-4-chloro-3,5-dimethoxy-1*H*-pyrazole (**4b**).

Compound **4b** was prepared from **3b** (218 mg, 1 mmole) and *N*-chlorosuccinimide (134 mg, 1 mmole) according to the procedure given for the synthesis of **4a**. Purification by plc (eluent: dichloromethane) afforded 207 mg (82%) of a slightly yellowish oil; ^{1}H-nmr (deuteriochloroform): δ 7.36-7.16 (m, 5H, Ph-H), 5.01 (s, 2H, NCH_2), 3.99 (s, 3H, C5-OCH_3), 3.92 (s, 3H, C3-OCH_3); ms: m/z (%) 252/254 (M^+, 60/20), 253 (10), 221 (18), 91 (100), 65 (15); high resolution ms: Calcd. for $C_{12}H_{13}ClN_2O_2$: 252.0666. Found: 252.0656 ± 0.0025, [14].

4-Bromo-3,5-dimethoxy-1-methyl-1*H*-pyrazole (**5a**).

To a mixture of bromine (480 mg, 3 mmoles) and sodium carbonate (636 mg, 6 mmoles) in 6 ml of dichloromethane were added dropwise 426 mg (3 mmoles) of **3a** in 5 ml of dichloromethane at 0°. After completion of the addition the reaction mixture was stirred for 30 minutes at 0°, then 30 ml of water was added. The dichloromethane phase was separated and the aqueous phase was extracted twice with 10 ml of dichloromethane. The combined organic phases was washed with water, dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was subjected to plc (eluent: dichloromethane) to afford 466 mg (70%) of a yellowish oil; ^{1}H-nmr (deuteriochloroform): δ 4.07 (s, 3H, C5-OCH_3), 3.89 (s, 3H, C3-OCH_3), 3.53 (s, 3H, NCH_3); ms: m/z (%) 220/222 (M^+, 100/92), 219/221 (35/41), 205/207 (66/56), 177/179 (21/20), 163/165 (32/30), 83 (34); high resolution ms: Calcd. for $C_6H_9BrN_2O_2$: 219.9848. Found: 219.9842 ± 0.0021, [14].

1-Benzyl-4-bromo-3,5-dimethoxy-1*H*-pyrazole (**5b**).

The preparation of compound **5b** from 480 mg (3 mmoles) of bromine and 655 mg (3 mmoles) of **3b** was carried out according to the procedure given for the synthesis of **5a**. Purification by plc (eluent: dichloromethane) gave 767 mg (86%) of a yellowish oil; ^{1}H-nmr (deuteriochloroform): δ 7.35-7.17 (m, 5H, Ph-H), 5.03 (s, 2H, NCH_2), 3.97 (s, 3H, C5-OCH_3), 3.92 (s, 3H, C3-OCH_3); ms: m/z (%) 296/298 (M^+, 59/60), 297 (13), 265/267 (16/18), 91 (100), 83 (14), 65 (14).

Anal. Calcd. for $C_{12}H_{13}BrN_2O_2$: C, 48.50; H, 4.41; N, 9.43. Found: C, 48.30; H, 4.28; N, 9.19.

3,5-Dimethoxy-4-iodo-1-methyl-1*H*-pyrazole (**6a**).

To a boiling mixture of **3a** (142 mg, 1 mmole), sodium acetate (180 mg, 2.2 mmoles) and water (1 ml) was added dropwise 996 mg (6 mmoles) of potassium iodide and 508 mg (2 mmoles) of iodine in 2 ml of water and the reaction mixture was then further heated to reflux for 10 minutes. After cooling, the mixture was made slightly alkaline by addition of sodium carbonate and was then exhaustively extracted with ether. The combined ether phases were dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was subjected to plc (eluent: dichloromethane) to give 195 mg (73%) of a yellowish oil; ^{1}H-nmr (deuteriochloroform): δ 4.04 (s, 3H, C5-OCH_3), 3.89 (s, 3H, C3-OCH_3), 3.57 (s, 3H, NCH_3); ms: m/z (%) 268 (M^+, 100), 267 (15), 253 (34), 211 (21), 83 (15).

Anal. Calcd. for $C_6H_9IN_2O_2$: C, 26.89; H, 3.38; N, 10.45. Found: C, 27.08; H, 3.66; N, 10.24.

1-Benzyl-3,5-dimethoxy-4-iodo-1*H*-pyrazole (**6b**).

The preparation of compound **6b** from 218 mg (1 mmole) of **3b** and 996 mg (6 mmoles) of potassium iodide and 508 mg (2 mmoles) of iodine was carried out according to the procedure given for the synthesis of **6a**. Purification by plc afforded 258 mg (75%) of a yellowish oil; ^{1}H-nmr (deuteriochloroform): δ 7.35-7.17 (m, 5H, Ph-H), 5.06 (s, 2H, NCH_2), 3.93 (s, 3H, C5-OCH_3), 3.91 (s, 3H, C3-OCH_3); ms: m/z (%) 345 (M^++1, 13), 344 (M^+, 100), 313 (14), 91 (58), 83 (14).

Anal. Calcd. for $C_{12}H_{13}IN_2O_2$: C, 41.88; H, 3.81; N, 8.14. Found: C, 42.10; H, 3.69; N, 8.01.

Reaction of **3a** with Sulfuryl Chloride.

To a solution of 426 mg (3 mmoles) of **3a** in 5 ml of ether were dropwise added 507 mg (3.75 mmoles) of sulfuryl chloride at 0° and the mixture was then stirred for 45 minutes at this temperature. After addition of water (10 ml) the ether phase was separated and the aqueous phase was extracted with two additional 5 ml portions of ether. The combined ether extracts were successively washed with saturated aqueous sodium carbonate solution and water, dried over anhydrous sodium sulfate and evaporated *in vacuo*. The residue was subjected to plc (eluent: dichloromethane) to afford 220 mg (37%) of 4,4-dichloro-2,4-dihydro-5-methoxy-2-methylpyrazol-3-one (**7**) as a light brown oil which solidified with time (mp 45-49°); ^{1}H-nmr (deuteriochloroform): δ 3.98 (s, 3H, C5-OCH_3), 3.26 (s, 3H, N2-CH_3); ^{13}C-nmr (deuteriochloroform): δ 163.5 (pyrazolone C-3 (= pyrazolone C=O), $^3J_{CO,NCH3}$ = 2.3 Hz), 159.5 (pyrazolone C-5, $^3J_{C5,OCH3}$ = 3.8 Hz), 67.5 (pyrazolone C-4), 56.7 (C5-OCH_3, ^1J = 148.8 Hz), 32.0 (N2-CH_3, ^1J = 141.0 Hz); ir (potassium bromide): cm^{-1} 1739 (C=O), 1628; ms: m/z (%) 196/198/200 (M^+, 67/46/6), 161/163 (100/34), 153/155/157 (27/18/3), 133 (15), 119/121 (25/9), 103/105 (23/8), 47 (11); high resolution ms: Calcd. for $C_5H_6Cl_2N_2O_2$: 195.9806. Found: 195.9803 ± 0.0020.

Acknowledgement.

The authors thank Mr. J. Dolezal, Institute of General Chemistry, Technical University of Vienna, for performing the high-resolution mass spectra.

REFERENCES AND NOTES

[1] Part of the planned Diploma Thesis of H. G., University of Vienna, 1995.

[2] J. Elguero, Comprehensive Heterocyclic Chemistry, Vol **5**, A. R. Katritzky and C. W. Rees, eds, Pergamon Press, Oxford, 1984, p 167, p 216.

[3] K. Hartke and X.-P. Popp, *Arch. Pharm. (Weinheim)*, **327**, 385 (1994).

[4] K. Hartke and H.-G. Müller, *Arch Pharm. (Weinheim)*, **321**, 863 (1988).

[5] Attempts to prepare **1** from dimethyl malonate and the Lawesson-reagent were not successful.

[6] R. Hüttel, O. Schäfer and P. Jochum, *Liebigs Ann. Chem.*, **593**, 200 (1955).

[7] A. Bax, *J. Magn. Reson.*, **57**, 314 (1984).

[8] S. Sarkar and A. Bax, *J. Magn. Reson.*, **62**, 109 (1985).

[9] T. Jippo, O. Kamo and K. Nagayama, *J. Magn. Reson.*, **66**, 344 (1986).

[10] H. Kalchhauser and W. Robien, *J. Chem. Inform. Comput. Sci.*, **25**, 103 (1985).

[11] SADTLER Collection, SADTLER Research Laboratories, Philadelphia, PA, USA.

[12] A. Echevarria, J. Elguero, G. I. Yranzo, E. Diez-Barra, A. de la Hoz, A. Moreno and M. A. Garcia-Martin, *J. Chem. Soc., Perkin Trans. I*, 2229 (1993).

[13] M. Begtrup, G. Boyer, P. Cabildo, C. Cativiela, R. M. Claramunt, J. Elguero, J. I. Garcia, C. Toiron and P. Vedsø, *Magn. Reson. Chem.*, **31**, 107 (1993).

[14] Repeated CHN-analysis of the oil gave correct values for H and N, however, the percentage values for C were always somewhat outside of the permitted range. Thus, elemental composition was proved by high resolution mass spectrometry.