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NMR, X-Ray and MS Investigations of Ethyl 2-Aroyl- and Ethyl 2-Arylcarbamoyl-4,5- dimethyl-1,2,3,6-tetrahydropyridazine-1- carboxylates: Flexible Multidentate Ligands

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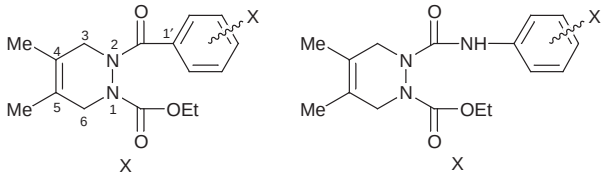
The ^{1}H and ^{13}C NMR spectral assignments of ethyl 2-aroyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine-1-carboxylates (**1a**–**1h**) and ethyl 2-arylcarbamoyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine-1-carboxylates (**2a**–**2k**) are given based on DQF COSY, ^{1}H,13C HMQC and 1H,^{13}C HMBC-measurements; the dynamics of the tetrahydropyridazine ring has been studied by ^{1}H, ^{1}H EXSY-technique and the structure of one congener (4′-methylphenyl-derivative, **2a**) has been confirmed by X-ray structure analysis.

[4 + 2] Cycloaddition of azo compounds and buta-1,3-diene leads to the formation of tetrahydropyridazines[1] which have been shown to exhibit some conformational flexibility.[2,3] When these starting compounds are substituted by appropriate heteroatom (N, O) containing groups, flexible multidentate ligands such as ethyl 2-aroyl- and ethyl 2-arylcarbamoyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine-1-carboxylates[4] are formed (Scheme 1). To our knowledge neither X-ray crystallographic nor NMR and MS characteristics of these conformationally flexible, biochemically interesting structures have as yet been reported. Therefore, we report now ^{1}H and ^{13}C NMR spectral assignments, X-ray crystallographic and MS studies of the series of ethyl 2-aroyl- and ethyl 2-arylcarbamoyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine-1-carboxylates available in our laboratories.



X	
1a	4-OMe
1b	4-Me
1c	H
1d	4-F
1e	2-F
1f	4-Cl
1g	3-NO_2
1h	4-NO_2

X	
2a	4-Me
2b	2-Me
2c	4-Et
2d	3-Me
2e	H
2f	4-Cl
2g	4-Br
2h	3-Cl
2i	4-OMe
2j	4-NO_2
2k	2-Cl

Scheme 1

The ^{1}H and ^{13}C NMR spectra of substituted ethyl 2-aroyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine-1-carboxylates (**1a**–**1h**) and ethyl 2-arylcarbamoyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine-1-carboxylates (**2a**–**2k**) have been assigned using DQF COSY[5,6] as well ^{1}H,^{13}C HMQC[7,8] and ^{1}H, ^{13}C HMBC-techniques.[9] The ^{13}C NMR chemical shifts of the aroylic C=O and *ipso*-carbon C1′ of the phenyl ring in **1a**–**1h** show significant correlations with Hammett σ substituent constants, IR stretching wavenumbers ν(C=O) and PM3 atomic charges q(C). Corresponding ^{13}C NMR correlations are valid in **2a**–**2k**. In addition, ^{1}H NMR chemical shifts of amido protons exhibit linear dependences with σ, ν(N–H) and q(NH). The diastereotopic protons of two CH_2-groups in the heterocycle are in dynamic equilibrium *via* simultaneous inversions of the nitrogens as detected by the ^{1}H, ^{1}H EXSY-technique.[11,12]

X-Ray crystallographic analysis of ethyl 2-(4′-methyl)-phenylcarbamoyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine-1--carboxylate **2a** reveals that the distortion of the heterocycle from planarity is strong in the crystalline state. The crystal packing of **2a** occurs as dimers *via* weak hydrogen bonding between the amido proton and esteric carbonyl.

Experimental

Crystal Data for **2a**.—$C_{17}H_{23}N_3O_3$, $M = 317.4$, $F(000) = 1360$, monoclinic, $a = 19.893(3)$, $b = 7.764(2)$, $c = 22.106(2)$ Å, $\beta = 93.98(1)^\circ$, $V = 3406(1)$ Å^3 (by least-squares refinement on diffractometer angles for 25 centered reflections, $\lambda = 0.71073$ Å), space group $C2/c$ (no. 15), $Z = 8$, $D_c = 1.24$ g cm^{-3}, μ(Mo-Kα) = 0.086 mm^{-1}. The experimental data were collected with an Enraf-Nonius CAD4 diffractometer with graphite monochromated Mo-Kα radiation ($\lambda = 0.71073$ Å) and ω–2θ scan mode. 3083 reflections measured (θ range from 2.1 to 25, h: 0–23, k: 0–9, l: −26 to 26), 2991 unique [merging $R = 0.0174$ after absorption correction] (ψ-scan absorption correction[13] was applied with minimum transmission of 0.932 and maximum transmission of 0.968) giving 2214 with $I > 2\sigma(I)$. Linear and approximated isotropic crystal decay, *ca.* 6.6%, corrected during processing.

The structure was solved using direct methods with SHELXS-97.[13] Full-matrix least-squares refinement was carried out using SHELXL-97[14] with all the non-hydrogen atoms refined anisotropically. Hydrogen atoms were located from electron density maps and refined anisotropically. The weighting scheme is $w = 1/[\sigma^2(F_o^2) + (0.0664P)^2 + 0.52P]$ where $P = [\mathrm{Max}(F_o^2, 0) + 2F_c^2]/3$. Final R and R_w values are 0.0393 and 0.1072 for data $I > 2\sigma(I)$ and 0.0579 and 0.1147 for all data.

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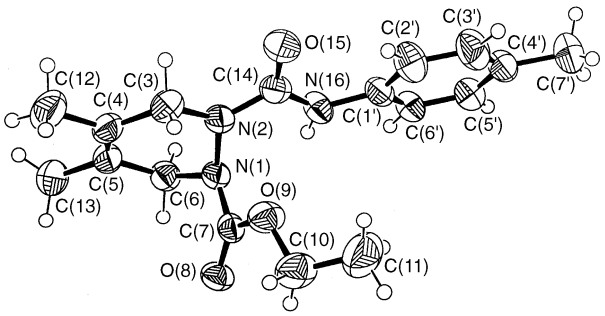

Fig. 2 An ORTEP-III picture[15] of the X-ray crystal structure of **2a**

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Techniques used: ^{1}H and ^{13}C NMR, DQF ^{1}H, ^{1}H COSY, ^{1}H, ^{1}H EXSY, ^{1}H, ^{13}C HMQ(B)C, MS, X-ray diffraction.

References: 16

Fig. 1: 500 MHz ^{1}H NMR spectrum of **2a** measured in $(CD_3)_2SO$ at 30 °C

Fig. 3: A Schakal97 picture[16] of the crystal packing of **2a**

Table 1: ^{1}H NMR chemical shifts (δ_H/ppm) of **1a**–**1h**

Table 2: ^{13}C NMR chemical shifts (δ_c/ppm) of **1a**–**1h**

Table 3: ^{1}H NMR chemical shifts (δ_H/ppm) of **2a**–**2k**

Table 4: ^{13}C NMR chemical shifts (δ_c/ppm) of **2a**–**2k**

Table 5: Correlation of NMR chemical shifts of **1a**–**1h** and **2a**–**2k** with Hammett σ substituent constants, [10] IR data[4] and PM3 atomic charges[4] of conformation **A**

Table 6: Experimental crystallographic data for ethyl 2-(4-methyl)phenylcarbamoyl-4,5-dimethyl-1,2,3,6-tetrahydropyridazine-1-carboxylate **2a**

Table 7: Bond lengths (Å) and angles (°) for **2a**

Table 8: Torsion angles for **2a**

Table 9: The main fragments in the 70 eV EI$^+$ mass spectra of **1a**–**1h**

Table 10: σ^+-values of the aryl substituent X *vs.* $[M^+]/[(M-K)^+]$ in **1a**–**1h**

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References cited in this synopsis

1 S. Weinreb, *Hetero Diels–Alder Methodology in Organic Synthesis,* Academic Press, New York, 1987.
2 J. E. Anderson and J.-M. Lehn, *Tetrahedron,* 1968, **24**, 137.
3 T. H. Fischer, J. C. Crook and S. Chang, *Tetrahedron,* 1987, **43**, 2443.
4 A. Perjéssy, P. Meyer, W.-D. Rudorf, D. Loos, A. Kolbe and I. Schaller, *Heterocyclic Commun.,* in print and references cited therein.
5 M. Rance, O. W. Sørensen, G. Bodenhausen, G. Wagner, R. R. Ernst and K. Wüthrich, *Biochem. Biophys. Res. Commun.,* 1984, **117**, 479.
6 A. Derome and M. Williamson, *J. Magn. Reson.,* 1990, **88**, 117.
7 A. Bax, R. H. Griffey and B. L. Hawkins, *J. Magn. Reson.,* 1983, **55**, 301.
8 A. Bax and S. Subramanian, *J. Magn. Reson.,* 1986, **67**, 565.
9 A. Bax and M. F. Summers, *J. Am. Chem. Soc.,* 1986, **108**, 2093.
11 J. Jeener, B. H. Meier, P. Bachman and R. R. Ernst, *J. Chem. Phys.,* 1979, **69**, 4546.
12 G. Wagner and K. Wüthrich, *J. Mol. Biol.,* 1982, **155**, 347.
13 G. M. Sheldrick, SHELXS-97, *Acta Crystallogr., Sect. A.,* 1990, **46**, 467.
14 G. M. Sheldrick, SHELXL-97–A Program for Crystal Structure Refinement, University of Göttingen, 1997.
15 M. N. Burnett and C. K. Johnson, Ortep-III: Oak-Ridge Thermal Ellipsoid Plot Program for Crystal Structure Illustrations, Oak Ridge National Laboratory ORNL-6895, 1996.
16 E. Keller, Schakal97/Windows 32, Kristallographisches Institut der Universität Freiburg, Germany, 1997.