

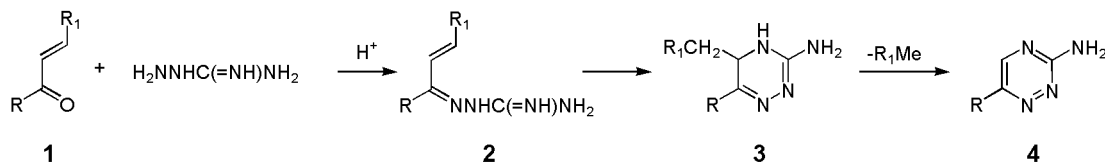
Jan Světlík* and Ladislav Šallai

Department of Pharmaceutical Analysis and Nuclear Pharmacy, Faculty of Pharmacy, Comenius University,
 Odbojarov 10, SK-832 32 Bratislava, Slovak Republic
 Received October 29, 2001

Cyclizations of α,β -unsaturated ketones with aminoguanidine under neutral conditions were examined. In contrast to literature reports of 1,2,4-triazines as reaction products, formation of 5-aryl-4,5-dihydro-3-methyl-1*H*-pyrazole-1-carboximidamides and carboxamides was observed. An explanation based on the Hard-Soft Acid-Base principle is presented and the probable causes of divergent reaction pathways are discussed.

J. Heterocyclic Chem., **39**, 363 (2002).

4-(2-Hydroxyphenyl)but-3-en-2-one (**1a**) is a unique α,β -unsaturated ketone, in that it contains an additional reactive site in the phenolic functional group. The ability of the hydroxyl group to undergo nucleophilic ring closure onto a preformed heterocyclic core is a key point in our syntheses of oxygen-bridged heterocycles. Based on butenone **1a**, we have previously prepared derivatives of pyridine, pyrimidine, benzodiazepine, benzothiazepine, thiazolo[3,2-*a*]pyrimidine, pyrimido[2,1-*b*]thiazine, pyrimido[2,1-*b*]thiazepine, and pyrido[2,3-*d*]pyrimidine [1]. Some of these conformationally locked molecules exhibit more complex structures arising from double-bridging or further annelation [2,3].



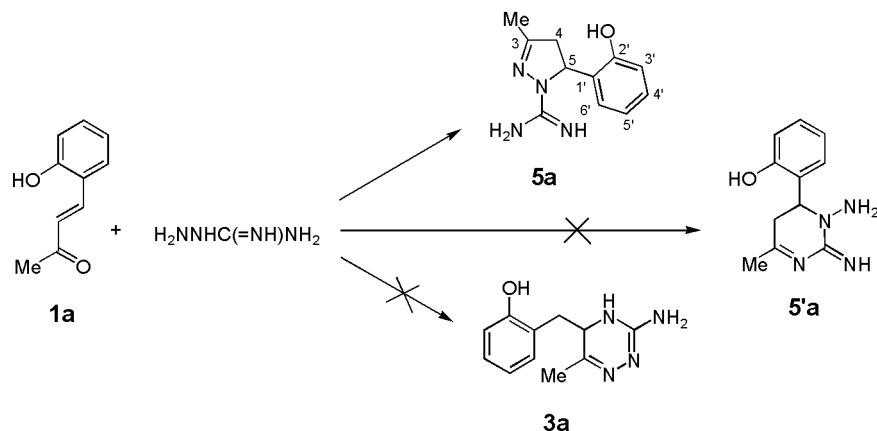
In collaboration with DuPont, it was found that certain pyrimidines bearing an O-bridge were active as inhibitors of acetylcholine esterase with arthropodicide activity [4]. Thus, low-cost starting materials (acetone and salicylaldehyde), simple preparation, and multigram-scale access render enone **1a** an attractive synthon for constructing novel heterocyclic compounds of potentially interesting chemical and medical properties.

Aminoguanidine is known to be an important bioactive substance. It belongs to potent inhibitors of nitric oxide synthase controlling the nitric oxide production in mammalian cells [5] and has become one of the promising agents for the treatment of diabetic complications [6]. On the other hand, due to its multifunctional nature, aminoguanidine can serve as a valuable component in heterocyclic synthesis. Seeking more effective aminoguanidine mimics, we decided to incorporate the aminoguanidine unit into a heterocyclic structure by our above-mentioned method of condensation with **1a**. We also present herein a convenient synthetic route to highly functionalized 2-pyrazolines.

Reactions of aminoguanidine with α,β -unsaturated ketones **1** including bis(alkylidene)- or bis(arylidene)acetone have been extensively studied in the past and thoroughly reviewed by Neunhoeffer [7-9]. The primary products in the synthetic pathway are amidinohydrazones **2** formed in acid media [10]. Upon heating they were converted into 5,6-disubstituted 3-amino-4,5-dihydro-1,2,4-triazines **3** which can eliminate the 5-alkyl or aralkyl group when treated with a base to yield fully aromatized triazines **4** (Scheme 1) [7-9].

To avoid isolating a condensation intermediate **2** we performed heterocyclization directly in the higher boiling solvent (*n*-butanol) but under neutral conditions. Surprisingly,

treatment of **1a** with aminoguanidine hydrogencarbonate gave an isomeric product whose spectral data were not compatible with the expected structure **3a** (Scheme 2). In spite of similar structural features, the compounds **3a** and **5a** obtained here differ in the arrangement of the building units. Namely, the observed long-range H,C-correlations from selective INEPT spectra did not fit the triazine model **3a**, while they clearly proved the HOC₆H₄CHCH₂C(=)CH₃ connectivity pattern. To complete the connectivity in the whole molecule, it remained only to link the recognized fragment to the aminoguanidine moiety. However, this required considering different reacting centres of the addends. Inspection of the literature revealed that condensation of aminoguanidine with ethyl acetoacetate [11] leading to pyrazolone **6** and diaminopyrimidine **7** (Scheme 3) could give us a lead for structure determination. According to these findings, our preceding experience with butenone **1a**, and the obtained spectral data, we postulated 4,5-dihydro-1*H*-pyrazole-1-carboximidamide **5a** and 5,6-dihydro-2*H*-pyrimidin-1-ylamine **5'a** as acceptable alternatives of the constitutional isomer **3a**.

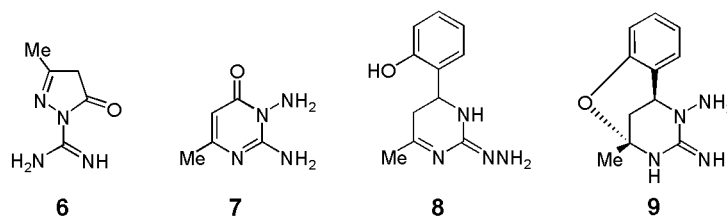


The results of the H,C-correlation nmr are compatible with both structures. Thus, upon irradiation of the respective aliphatic protons the following interactions were determined: 4-H_{a,b} – C-3, C-1'; 5-H – C-3, C-1', C-6' and H of Me – C-4 (numbering for **5a**). Evidently, the last two of the six detected polarization transfers cannot be referred to the corresponding H,C-nuclei pairs in triazine **3a** because only $^2J_{CH}$ and $^3J_{CH}$ are observable. An additional support for **5a** and **5'a** came from the resolution enhanced 1H nmr spectrum wherein a splitting between CH₃ and 4-H_b protons with $^4J=1.0$ Hz was found. Note that an analogous coupling over five saturated bonds in **3a** would be rather unusual. Another important fact followed from the analysis of the ABX system of the CH₂CH segment. The magnitudes of the geminal and vicinal couplings closely resembled to those reported for 1,3,5-trisubstituted 2-pyrazolines [12].

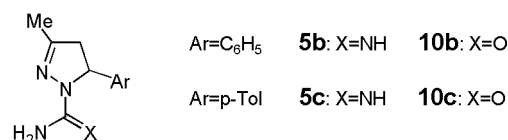
The mass spectrum of the product furnished a significant proof of the amidine structure **5a**. The prominent peaks at m/z 201, 176 and 175 were produced by loss of neutral molecules of NH₃ and HN=C=NH and the HN=C-NH₂ radical from the molecular ion (m/z 218), the primary cleavage modes being typical of N-substituted guanidines [13]. In addition, the second most abundant peak at m/z 83, (C₄H₇N₂)⁺, was a clue that indicated a 3-methylpyrazolinium species.

Since we anticipated largely the formation of oxygen-bridged pyrimidine **9** or a similar compound derived from **8**, attempts have been made to detect them (Scheme 3). However, in spite of our efforts, the hydroxyphenyl derivative **5a** was the only detectable product.

In order to find additional support for the studied heterocyclization, we employed two other arylidenes as a starting material for the synthesis. However, under similar conditions 4-phenyl- and 4-(4-methylphenyl)but-3-en-2-one (**1b** and **1c**) gave rise to two types of products having similar nmr spectral parameters. Remarkably, the condensations with **1b** and **1c** were accompanied with evolution of ammonia. The elemental composition of compounds **10b,c**, which crystallized from the reaction mixture, indicated a substitution of an O atom for the NH group when compared with the expected amidines **5b,c**, suggesting thus formation of amide analogues (Scheme 4). The target pyrazoles **5b,c** were isolated from the filtrates upon further work-up. Interestingly, these amidines, according to nmr analysis, were obtained as acetate salts (**5b,c** · CH₃COOH). The solvate formation had to be the result of a decomposition of ethyl acetate used as a crystallization solvent. The obvious reason why only derivatives **5b,c** suffered hydrolysis into **10b,c** lies in their solubility in *n*-butanol whereas hydroxyphenylpyrazole **5a**



It should be noted that there is another possible isomeric structure **8** which may satisfy the nmr data (Scheme 3). Nevertheless, the above fragmentation pattern, additional chemical evidence of **5a** via ring closure reactions [14] and results from single-crystal X-ray diffraction for analogous derivatives (see below) ruled out variant **8**.



was insoluble and precipitated from the reaction mixture and thus remained intact. Moreover, unlike compounds **5b,c**, amidine **5a** proved to be stable in solution.

Tolyl derivatives **5c** and **10c** turned out to be well crystallizing compounds so that we could grow suitable samples for X-ray analysis. The X-ray molecular structures represent the ultimate proof of the unusual products from the well known reaction [7-9] and will be published elsewhere [15].

The direction in which the observed heterocyclizations proceed depends on the reaction conditions used. As to the triazine pathway, open-chain amidinohydrazones **2** are produced by a nucleophilic 1,2-addition while the carbonyl group of the conjugated system **1** is attacked by the terminal hydrazine nitrogen of the reactant. The reaction mode of the key step under acid catalysis is controlled by protonation, which occurs at the imine nitrogen as evidenced by the X-ray structure of the aminoguanidine salt [16]. Due to the extensive delocalization of the positive charge over the guanidyl group in the monocation form [16,17], an intervention *via* the former nitrogen atom of the aminoguanidine will hence be favored.

By contrast, a competitive 1,4-addition becomes operative in the first stage of our pyrazole route. Evidently, such a Michael-type reaction has to involve an initial attack by the aminoguanidine internal hydrazine nitrogen at the electrophilic C-3 of enone **1**. Our explanation in terms of the HSAB concept relies on the assumption that the intervening species should be actually a free aminoguanidine molecule, as the hydrogencarbonate salt liberates vigorously CO₂ when heated with **1** at the beginning of the reaction. Hence, the reaction conditions are practically basic and typical of a conjugate addition. According to the recent quantum chemical studies on the aminoguanidine free base, [18] the endiamine form, H₂NN=C(-NH₂)NH₂, was found to be the most stable tautomer in the gas phase. Moreover, internal imine nitrogen bears the greatest negative charge [18] as calculated by the B3-LYP/6-31G(d) method. With respect to the reported findings we presume that this key hydrazine/imine nitrogen should become more polarizable and would be therefore a somewhat softer donor than the terminal one. This soft acid - soft base interaction of the olefinic β -carbon, possessing usually the largest LUMO coefficient [19], and the mentioned nitrogen will be a determining factor of the reaction. However, in this case it would be useful to know the solvent effects on the tautomer population in solution, that may affect the energy difference between the endiamine and imidiamide form H₂NNHC(=NH)NH₂ (approximately 5 kcal/mol in the gas phase [18]). Finally, the presented heterocyclization is completed by attack of the terminal hydrazine nitrogen at the carbonyl group in the initial Michael adduct.

EXPERIMENTAL

The melting points (uncorrected) were determined with a Kofler hot stage microscope. The ir spectra were recorded on a Nicolet Impact 400 D spectrophotometer. The EI mass spectra were obtained on a Jeol JMS D-100 instrument operating at 75 eV. Peak matching with perfluorokerosene as the reference was utilized for accurate mass measurements by hrms. The nmr spectra were measured on a Bruker AC-400 spectrometer with a dual ¹H/¹³C probe (400.136 MHz for ¹H and 100.614 MHz for ¹³C) for **5a** and Varian VXR-300 (299.943/75.429 MHz) for **5b,c** and **10b,c**.

The butenones were prepared according to the literature: **1a** [20], **1b** [21], **1c** [22].

General Procedure for the Preparation of Pyrazolines **5a-c** and **10b,c**.

A suspension of butenone **1a-c** (10 mmoles) and aminoguanidine hydrogencarbonate (1.36 g, 10 mmoles) in *n*-butanol (30 ml) was refluxed under stirring for 3 hours. The precipitated product **5a** was isolated by filtration, washed with *n*-butanol, and dried. For **1b,c** the reaction mixture (a solution formed after 2 hours) was concentrated on a vacuum rotary evaporator, the syrupy residue dissolved in ethyl acetate (10 ml) and left to stand at room temperature. The crystallized products **10b,c** were collected by filtration. The pyrazolines **5b,c** precipitated from the mother liquors upon standing.

4,5-Dihydro-5-(2-hydroxyphenyl)-3-methyl-1H-pyrazole-1-carboximidamide (**5a**).

This compound was obtained in 74 % yield (1.62 g), mp 249-251° (DMF); ir (potassium bromide): 3447 (NH₂), 3350-2450 (assoc. OH, NH₂, NH), 1670 (exo C=N), 1622 (C=N, NH₂ bend), 1472 (CH₂ bend), 1449 (CH₃ bend), 1304, 862, 750 (o-C₆H₄-wag) cm⁻¹; ¹H nmr (DMSO-d₆): δ 2.12 (s, 3H, Me), 3.08 (dd, 1H, J_{AB}=18.6 and J_{AX}=4.2 Hz, 4-H_a), 3.45 (ddd, 1H, J_{AB}=18.6, J_{BX}=11.8 and J_{BMe}=1.0 Hz, 4-H_b), 5.45 (dd, 1H, J_{AX}=4.2 and J_{BX}=11.8 Hz, 5-H), 5.70-7.20 (br, 4H, OH, NH₂, NH), 6.36 (dt, 1H, J=7.3 and 1.3 Hz, 5'-H), 6.43 (dd, 1H, J=8.1 and 1.2 Hz, 3'-H), 6.93 (m, 1H, 6'-H), 6.94 (m, 1H, 4'-H); ¹³C nmr (DMSO-d₆): δ 15.0 (Me), 43.1 (CH₂), 54.0 (CH), 114.0 (CH-3'), 118.9 (CH-5'), 125.8 (CH-6'/CH-4'), 127.0 (C-1'), 128.4 (CH-4'/CH-6'), 154.3 (C-2'), 155.9 (C-3), 162.1 (N-C=N); ms: *m/z* (relative intensity) 219 (6), 218 (C₁₁H₁₄N₄O, M⁺, 33), 201 (13), 177 (13), 176 (22), 175 (C₁₀H₁₁N₂O, 37), 160 (11), 146 (13), 145 (C₁₀H₉O, 100), 135 (14), 125 (14), 120 (16), 118 (23), 91 (13), 83 (C₄H₇N₂, 80), 77 (13), 65 (10), 58 (31), 43 (22), 42 (31).

Anal. Calcd. for C₁₁H₁₄N₄O: C, 60.53; H, 6.47; N, 25.67. Found: C, 60.71; H, 6.42; N, 25.39.

4,5-Dihydro-3-methyl-5-phenyl-1H-pyrazole-1-carboximidamide Acetate (**5b**).

Compound **5b** was obtained in 14 % yield (0.28 g), mp 227-229° (DMF); ir (potassium bromide): 3321 (NH₂, NH), 1667 (C=N), 1590 (COO), 1407, 765 (C₆H₅-wag), 695 cm⁻¹; ¹H nmr (DMSO-d₆): δ 1.60 (s 3H, Me of HOAc), 2.04 (s, 3H, Me), 2.76 (dd, 1H, J_{AB}=18.3 and J_{AX}=3.3 Hz, 4-H_a), 3.64 (dd, 1H, J_{AB}=18.3 and J_{BX}=11.7 Hz, 4-H_b), 5.51 (dd, 1H, J_{AX}=3.3 and J_{BX}=11.7 Hz, 5-H), 7.14 (dd, 2H, J=7.0 and 1.1 Hz, H_{ar}), 7.30-7.40 (m, 3H, H_{ar}), 7.8-10.0 (br, 4H, NH₂); ¹³C nmr (DMSO-d₆): δ 15.5 (Me), 25.0 (Me of HOAc), 47.5 (CH₂), 59.3 (CH), 125.3 (CH-2' + CH-6'), 127.9 (CH-4'), 128.9 (CH-3' + CH-5'), 140.4 (C-1'), 153.6 (C-3),

158.6 (N-C=N), 176.0 (CO of HOAc); ms: m/z (relative intensity) 202 ($C_{11}H_{14}N_4$, M^+ , 5), 201 (3), 185 ($C_{11}H_{11}N_3$, 4), 184 (3), 162 (6), 161 (60), 160 (36), 159 ($C_{10}H_{11}N_2$, 49), 145 (5), 144 (7), 119 (8), 115 (10), 104 (31), 93 (15), 91 (17), 83 ($C_4H_7N_2$, 100), 82 (13), 78 (18), 77 (24), 65 (8), 63 (6), 60 (22), 56 (16), 51 (18), 45 (35), 43 (55), 42 (42), 41 (16), 39 (15).

Anal. Calcd. for $C_{13}H_{18}N_4O_2$: C, 59.53; H, 6.92; N, 21.36. Found: C, 59.79; H, 7.09; N, 21.13.

4,5-Dihydro-3-methyl-5-phenyl-1H-pyrazole-1-carboxamide (**10b**).

Compound **10b** was obtained in 37% yield (0.75 g), mp 194–197° (dioxane-ethyl acetate); ir (potassium bromide): 3337 + 3185 (NH_2), 1655 (C=O), 1603 (C=N), 760 (C_6H_5 -wag), 703 cm^{-1} ; 1H nmr (DMSO- d_6): δ 2.06 (s, 3H, Me), 2.78 (dd, 1H, $J_{AB}=18.3$ and $J_{AX}=3.0$ Hz, 4- H_a), 3.67 (dd, 1H, $J_{AB}=18.3$ and $J_{BX}=11.8$ Hz, 4- H_b), 5.54 (dd, 1H, $J_{AX}=3.0$ and $J_{BX}=11.8$ Hz, 5-H), 7.15 (dd, 2H, $J=7.2$ and 1.2 Hz, H_{ar}), 7.29–7.41 (m, 3H, H_{ar}), 7.50–9.60 (br, 2H, NH_2); ^{13}C nmr (DMSO- d_6): δ 15.5 (Me), 47.5 (CH_2), 59.4 (CH), 125.3 (CH-2' + CH-6'), 128.0 (CH-4'), 128.9 (CH-3' + CH-5'), 140.3 (C-1'), 153.4 (C-3), 159.1 (CO); m/s: m/z (relative intensity) 203 ($C_{11}H_{13}N_3O$, M^+ , 22), 202 (7), 185 ($C_{11}H_{11}N_3$, 3), 184 (3), 161 (61), 160 (85), 159 ($C_{10}H_{11}N_2$, 70), 145 (7), 129 (7), 128 (7), 119 (9), 118 (9), 115 (9), 104 (43), 93 (8), 91 (10), 83 ($C_4H_7N_2$, 100), 82 (12), 78 (13), 77 (21), 65 (8), 63 (7), 51 (15), 43 (20), 42 (39), 39 (14).

Anal. Calcd. for $C_{11}H_{13}N_3O$: C, 65.01; H, 6.45; N, 20.67. Found: C, 64.83; H, 6.61; N, 20.54.

4,5-Dihydro-3-methyl-5-(4-methylphenyl)-1H-pyrazole-1-carboximidamide Acetate (**5c**).

Compound **5c** was obtained in 20% yield (0.42 g), mp. 220–221° (DMF); ir (potassium bromide): 3314 (NH_2 , NH), 1666 (C=N), 1589 (COO), 1407, 809 ($p-C_6H_4$ -wag) cm^{-1} ; 1H nmr (DMSO- d_6): δ 1.61 (s, 3H, Me of HOAc), 2.04 (s, 3H, Me), 2.28 (s, 3H, Me-Tol), 2.74 (dd, 1H, $J_{AB}=18.3$ and $J_{AX}=3.5$ Hz, 4- H_a), 3.62 (dd, 1H, $J_{AB}=18.3$ and $J_{BX}=11.3$ Hz, 4- H_b), 5.46 (dd, 1H, $J_{AX}=3.5$ and $J_{BX}=11.3$ Hz, 5-H), 7.04 (AA' part of AA'BB', 2H, $J=8.1$ Hz, 3'-H + 5'-H), 7.18 (BB' part of AA'BB', 2H, $J=8.1$ Hz, 2'-H + 6'-H), 7.30–10.80 (br, 4H, NH_2); ^{13}C nmr (DMSO- d_6): δ 15.5 (Me), 20.6 (Me-Tol), 25.0 (Me of HOAc), 47.4 (CH_2), 59.2 (CH), 125.2 (CH-2' + CH-6'), 129.4 (CH-3' + CH-5'), 137.2 + 137.5 (C-1', C-4'), 153.6 (C-3), 158.4 (N-C=N), 176.0 (CO of HOAc).

Anal. Calcd. for $C_{14}H_{20}N_4O_2$: C, 60.85; H, 7.29; N, 20.27. Found: C, 60.99; H, 7.59; N, 20.02.

4,5-Dihydro-3-methyl-5-(4-methylphenyl)-1H-pyrazole-1-carboxamide (**10c**).

Compound **10c** was obtained in 26% yield (0.27 g), mp 198–201° (dioxane); ir (potassium bromide): 3246 (NH_2), 1673 (C=O), 1597 (C=N), 814 ($p-C_6H_4$ -wag) cm^{-1} ; 1H nmr (DMSO- d_6): δ 2.05 (s, 3H, Me), 2.28 (s, 3H, Me-Tol), 2.75 (dd, 1H, $J_{AB}=18.3$ and $J_{AX}=3.0$ Hz, 4- H_a), 3.64 (dd, 1H, $J_{AB}=18.3$ and $J_{BX}=11.7$ Hz, 4- H_b), 5.50 (dd, 1H, $J_{AX}=3.0$ and $J_{BX}=11.7$ Hz, 5-H), 7.04 (AA' part of AA'BB', 2H, $J=8.1$ Hz, 3'-H + 5'-H), 7.18 (BB' part of AA'BB', 2H, $J=8.1$ Hz, 2'-H + 6'-H), 7.60–10.20 (br, 2H, NH_2); ^{13}C nmr (DMSO- d_6): δ 15.5 (Me), 20.6 (Me-Tol), 47.5 (CH_2), 59.2 (CH), 125.2 (CH-2' + CH-6'), 129.4 (CH-3' + CH-5'), 137.3 (C-1' + C-4'), 153.4 (C-3), 159.1 (CO).

Anal. Calcd. for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.37. Found: C, 66.20; H, 7.02; N, 19.53.

Acknowledgements.

This work was supported by the Grant Agency of the Slovak Republic (# 1/8215/01). The author wishes to thank Dr. V. Hanus of the Heyrovsky Institute of Physical Chemistry, Prague, for measuring the mass spectra.

REFERENCES AND NOTES

- [*] E-mail: svetlik@fpharm.uniba.sk
- [1a] J. Svetlik, F. Turecek and V. Hanus, *J. Chem. Soc., Perkin Trans. I*, 563 (1987); [b] J. Svetlik, F. Turecek and V. Hanus, *J. Chem. Soc., Perkin Trans. I*, 2053 (1988); [c] J. Svetlik, V. Hanus and J. Bella, *Liebigs Ann. Chem.*, 91 (1989); [d] J. Svetlik, I. Goljer and F. Turecek, *J. Chem. Soc., Perkin Trans. I*, 1315 (1990); [e] J. Svetlik, V. Hanus and J. Bella, *J. Chem. Res. (S)*, 4 (1991).
- [2] J. Svetlik, T. Liptaj and F. Turecek, *J. Heterocyclic Chem.*, **36**, 209 (1999).
- [3] J. Svetlik and T. Liptaj, *J. Heterocyclic Chem.*, **36**, 1023 (1999).
- [4] S. F. McCann and B. L. Finkelstein, PCT Int. Appl. WO 9946,266 (1999); *Chem. Abstr.*, **131**, 214308d (1999).
- [5] O. W. Griffith and S. S. Gross, in *Methods in Nitric Oxide Research*, M. Feelisch and J. S. Stamler, eds., John Wiley & Sons, Chichester, 1996, pp 187–208.
- [6] R. Bucala, A. Cerami and H. Vlassara, *Diabetes Rev.*, **3**, 258 (1995).
- [7] H. Neunhoffer and P. F. Wiley, in *The Chemistry of Heterocyclic Compounds*, Vol. **33**, A. Weissberger and E. C. Taylor, eds., Wiley-Interscience, New York, 1978, pp 360 and 600.
- [8] H. Neunhoffer, in *Comprehensive Heterocyclic Chemistry*, Vol. **3**, Part **2B**, A. R. Katritzky and C. W. Rees, eds., Pergamon Press, Oxford, 1984, pp 432–435.
- [9] H. Neunhoffer, in *Comprehensive Heterocyclic Chemistry II*, Vol. **6**, A. R. Katritzky, C. W. Rees and E.F.V. Scriven, eds., Pergamon, New York, 1996, p. 559.
- [10] T. Nishimura, C. Yamazaki, H. Toku, S. Yoshii, K. Hasegawa, M. Saito and D. Nagaki, *Chem. Pharm. Bull.*, **22**, 2444 (1974).
- [11] J. J. Hlavka, P. Bitha, Y. Lin and T. Stohmeyer, *J. Heterocyclic Chem.*, **21**, 1537 (1984).
- [12] W. Bruegel, *Handbook of NMR Spectral Parameters*, Vol. **3**, Heyden, London, 1979, p 640.
- [13] J. H. Beynon, J. A. Hopkinson and A. E. Williams, *Org. Mass. Spectrom.*, **1**, 169 (1968).
- [14] J. Svetlik and T. Liptaj, *J. Heterocyclic Chem.*, in preparation.
- [15] V. Kettmann and J. Svetlik, *Acta Crystallogr., Sect. C*, in preparation.
- [16] J. T. Koskinen, M. Koskinen, I. Mutikainen, B. Mannfors and H. Elo, *Z. Naturforsch.*, **51B**, 1771 (1996).
- [17] M. Koskinen, I. Mutikainen, P. Tilus, E. Peltari, M. Korela and H. Elo, *Monatsh. Chem.*, **128**, 767 (1997).
- [18] J. T. Koskinen, M. Koskinen, I. Mutikainen, P. Tilus, B. Mannfors and H. Elo, *Z. Naturforsch.*, **52B**, 1259 (1997).
- [19] I. Fleming, *Frontier Orbitals and Organic Chemical Reactions*, John Wiley & Sons, Chichester, 1978, pp 70–72.
- [20] C. D. Harries, *Ber.*, **24**, 3180 (1891).
- [21] N. L. Drake and P. Allen, in *Org. Synth.*, Coll. Vol. **1**, H. Gilman and A.H. Blatt, eds., John Wiley & Sons, New York, 1948, p 77.
- [22] S. J. Kesten, M. J. Degnan, J. Hung, D. J. McNamara, D. F. Ortwine, S. E. Uhlenndorf and L. M. Werbel, *J. Med. Chem.*, **35**, 3429 (1992).