Pergamon

Tetrahedron Letters, Vol. 35, No. 37, pp. 6909-6912, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01417-5

Novel Tandem Cyclization-Oxidation Reaction of 2,2-Dimethylpenta-3,4-dienal Hydrazones

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Abstract: **Synthesis of 3-substituted 2,2-dimethyl-penta-3,4-dienal hydrazones, their cyclization and following easy oxidation is reported. Reaction appears to be a new synthetic pathway for preparation of subetituted 2,3,4,5-tetrahydro-pyridazin-3-ones.**

We report the cyclization of 3-substituted 2,2-dimethylpenta-3,4-dienal hydrazones **1** followed by the very easy oxidation leading to the formation of pyridazinone derivatives **2**[1] (Figure 1). They are formed as mixtures of *5R* and *5S* enantiomers.

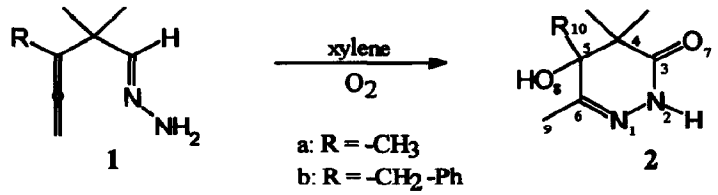

Figure 1

We have already published the reaction of homoallenylaldehyde with hydrazine hydrate leading to azine. This under heating entered into an intramolecular "criss-cross" cycloaddition reaction forming a tetracyclic structure[2]. During the study of that reaction we have isolated a by-product, 5-substituted 4,4,6-trimethyl-2,3,4,5-tetrahydropyridazin-3-one (**2**), whose yield depends on the time of the oxidation.

The structure of the pyridazinones was established on the basis of MS, ^{1}H- and ^{13}C-NMR spectroscopy[1], including long-range COSY, HETCOR and long-range HETCOR[3]. X-ray structural analysis[4] supported our findings and showed the situation in the solid state and the crystal packing. The crystallization of compounds **2** from methanol or chloroform led to the formation of crystals with crystallinic solvent. Crystals without solvent were formed from acetone and ethylacetate.

A proposed mechanism of the compound **2** formation is shown on Figure 2.

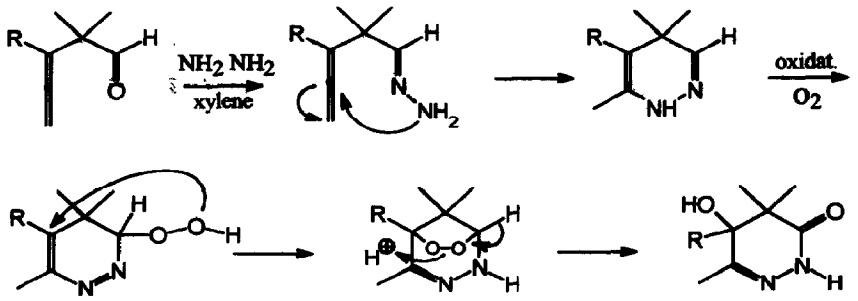

Figure 2

The first step is supposed to be a hydrazone formation. Then a cyclization starting by the attack of the nitrogen atom to the central allenic carbon atom occurs with formation of a pyridazine skeleton. The peroxide formed as a hypothetical intermediate corresponds to the product of oxidation[5]. Following ring-closure, O-O bond-cleavage gave rise to a very stable pyridazinone product.

Some pyridazinone derivatives were successfuly tested as a novel anxiolitics. Moreover, an amebacidal activity of pyridazin-3-ones was observed[6]. This cyclization might be a new synthetic method for the preparation of substituted pyridazinones when the reaction mechanism will be learnt and the yield by setting favourable conditions improved.

Further studies will confirm the hypothesis of the reaction mechanism and show the general application of such a type of synthesis.

References and notes

1a. 5-hydroxy-4,4,5,6-tetramethyl-2,3,4,5-tetrahydropyridazin-3-one (**2a**)

Preparation

2,2-dimethyl-penta-3,4-dienals were prepared according to the method of B. Thomson (U. S. 3,236,869; *Chem. Abst.*, **1966**, 64, 17428).

A mixture of 2,2,3-trimethylpenta-3,4-dienal, three equivalents of hydrazin monohydrate, catalytic amount of p-TSA and benzene was refluxed under Dean-Stark apparatus. After the separation of water ceased benzene was evaporated and the residue dissolved in xylene and refluxed for 5h. Then xylene was evaporated, the residue dissolved in methanol and the formed crystals filtered off.

mp 194-195°C (ethylacetate);

MS (CI): 188 (2.9, M+NH_4), 172 (10.6), 171 (100, M+H), 170 (3.7), 127 (3.5)

IR (KBr, cm^{-1}): 730, 770 (m) ,825, 925, 1070 (m), 1110 (s), 1160(m), 1205(m), 1230, 1280, 1340 (m), 1385 (s), 1430 (m), 1465, 1665 (s, C=N), 2980 (m), 3090 (m), 3230(s)

^1H NMR (400MHz, acetone-d_6, δ): 1.03 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.19 (3H, s, CH_3(10)), 1.98 (3H, s, CH_3(9)), 4.30 (1H, s, OH), 9.5 (1H, bs, NH)

^{13}C NMR (100MHz, acetone-d_6, δ): 16.27, 18.27 (C9), 19.58 (C10), 20.12, 44.03 (C4), 74.09 (C5), 159.56 (C6), 174.36 (C3)

1b. 5-benzyl-5-hydroxy-4,4,6-trimethyl-2,3,4,5-tetrahydropyridazin-3-one (**2b**)

Preparation
5-benzyl-5-hydroxy-4,4,6-trimethyl-2,3,4,5-tetrahydropyridazin-3-one was prepared according to the method 1a. mp (with crystallinic methanol) 168-171°C;
MS (CI): 249 (1.8), 248 (16.6), 247 (100, M+H), 155 (12), 113 (23.1), 91 (21.1)
^1H NMR (400MHz, acetone-d_6, δ): 1.01 (3H, CH_3); 1.11 (3H, CH_3); 1.13 (3H, CH_3); AB pattern centered at 2.89 (2H, CH_2, δ_A=2.85, δ_B=2.93, J=13); 4.17 (1H, s, OH), 7.18-7.26 (5H, m, Ar-H), 9.6 (1H, bs, NH)
^{13}C NMR (100MHz, acetone-d_6, δ): 15.93, 20.35, 20.68, 39.65, 44.87 (C4), 77.77 (C5), 127.37 (C16), 128.61 (C14, C15), 131.36 (C12, C13), 137.57 (C11), 159.03 (C6), 174.64 (C3)

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Tetrahedron Lett., **1993**, 34 (No 51), 8341

3. *NMR* spectroscopy

The data were recorded on 400 MHz Varian Unity spectrometer. For measurements of 2D spectra standard pulse sequences were used. Due to the high substitution grade of the heterocyclic ring the only long-range COSY variant (τ=0.6 sec.) was applied for **2a** and it gave correlation between the two geminal methyl groups. Carbon signals directly bound to the hydrogens could be assigned by HETCOR ($^1J_{CH}$=140Hz). Long-range HETCOR ($^1J_{CH}$=140Hz, $^nJ_{CH}$=7Hz) provided us with additional information and showed correlations among the hydrogens of those two methyl groups and carbons C5, C3 and C4. The hydrogens of other two methyl groups at C5 and C6 correlated with carbons C5, C4 and C6, C5, respectively. A correlation of the hydroxy group with the geminal methyl group at C5 even appeared in L. R. COSY as well as in L. R. HETCOR (although the last one was very weak and the only one under these conditions). All NMR spectra are available on request from authors RM and ADG.

4. *X-ray* structural analysis

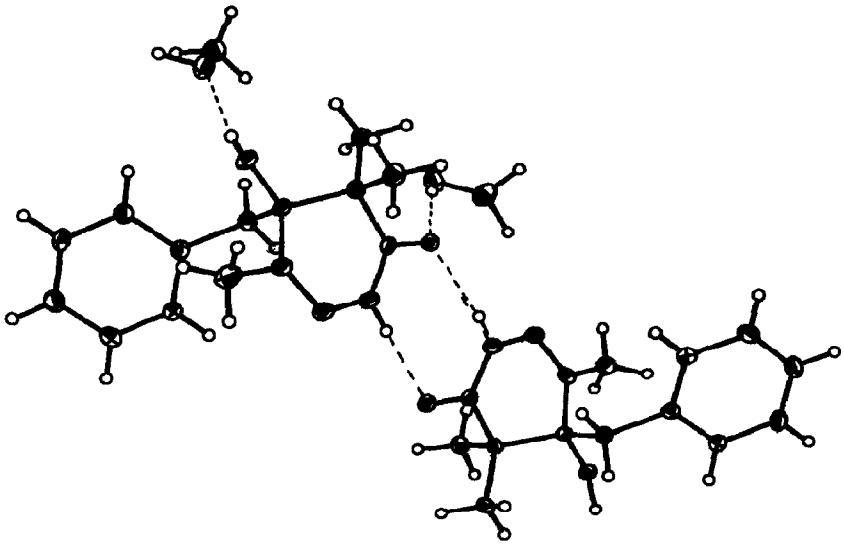
The data were collected with KUMA KM-4 kappa axis four-circles diffractometer. The structures were solved by direct methods using SHELXS-86 (Sheldrick, G.M. *Acta Cryst.* **1990**, A46, 467) and refined on F^2 for all reflections using SHELXL-93 (Sheldrick, G.M. **1993**). The tables of atomic coordinates of all atoms including hydrogens, anisotropic temperature displacement factors and the full list of interatomic distances and angles were deposited and can be obtained upon request from the author JM.

5-hydroxy-4,4,5,6-tetramethyl-2,3,4,5-tetrahydropyridazin-3-one (**2a**)

The compound is monoclinic with a=6.098(2), b=13.657(6), c=11.367(4) A, β=101.67(4)°, V=927.1(6) A^3, S. G. $P2_1/n$, Z=4, D_X=1.220 mgm^{-3}, M_0K_α=0.71073 A, 2545 rfl. total, R=0.0470 for obs. rfl with $I_0>2\sigma(I_0)$. Selected interatomic distances and angles are: N1-N2 1.394, N2-C3 1.337, C3-C4 1.508, C4-C5 1.538, C5-C6 1.510, C6-N1 1.273, C3-O7 1.221, C5-O8 1.418, C6-C9 1.492, C5-C10 1.525 A,

N1-N2-C3 125.8, N2-C3-C4 116.5, C3-C4-C5 109.1, C4-C5-C6 108.7, C5-C6-N1 122.6, C6-N1-N2 116.8, N2-C3-O7 120.8, N1-C6-C9 117.9, C6-C5-O8 108.5, C6-C5-C10 106.9°.

5-benzyl-5-hydroxy-4,4,6-trimethyl-2,3,4,5-tetrahydropyridazin-3-one . CH_3OH (**2b**)



Crystal packing of compound **2b**.

The compound is monoclinic with a=10.529(2), b=17.397(3), c=16.846(3) A, β=98.29(3)°, V=3053.5(10) A^3, S. G. $P2_1/c$, Z=8, D_x=1.211 mgm^{-3}, M_oK_α=0.71073 A, 5695 rfl. total, R=0.0568 for obs. rfl with $I_o>2\sigma(I_o)$. There are two independent molecules in the asymmetric unit of the crystal with opposit configuration on the chiral centre. Selected averaged interatomic distances and angles are: N1-N2 1.388, N2-C3 1.333, C3-C4 1.503, C4-C5 1.547, C5-C6 1.515, C6-N1 1.274, C3-O7 1.246, C5-O8 1.406, C6-C9 1.493, C5-C10 1.541, C10-C11 1.510 A, N1-N2-C3 126.6, N2-C3-C4 115.8, C3-C4-C5 107.1, C4-C5-C6 107.2, C5-C6-N1 121.9, C6-N1-N2 116.0, N2-C3-O7 120.3, N1-C6-C9 117.5, C6-C5-O8 108.0, C6-C5-C10 109.3°.

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Acknowledgements: The authors are grateful to prof. Dr. Roger Dommisse (Antwerp University) for his kind consent to record 2D NMR spectra.

(*Received in UK* 24 *May* 1994; *revised* 18 *July* 1994; *accepted* 22 *July* 1994)