Monatshefte für Chemie 135, 435–439 (2004)
DOI 10.1007/s00706-003-0092-3

Monatshefte für Chemie
Chemical Monthly
Printed in Austria

On the Synthesis of 3-Acetyl-1-aryl-1,4,5,6-tetrahydro-1*H*-1,2,4-triazepin-7-ones by Reaction of Nitrilimines with 3-Aminopropanoic Acid

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Received July 30, 2003; accepted August 6, 2003
Published online February 5, 2004

Summary. Nitrilimines were prepared from *N*-arylhydrazono chlorides and reacted with β-alanine yielding the corresponding amidrazones, which were treated with 1,1′-carbonyldiimidazole in *THF* affording the hitherto unknown 3-acetyl-1-aryl-1,4,5,6-tetrahydro-1,2,4-triazepin-7-ones.

Keywords. Arylacetonitrilimines; 1,2,4-Triazepin-7-ones; Cyclization.

Introduction

The highly reactive nitrilimines **2** are potent intermediates in heterocyclic syntheses by 1,3-dipolar cycloaddition reactions [1], by cyclocondensations [2–4], or by 1,3-electrophilic additions with nucleophiles [5]. In a preceding paper we reported about the synthesis of 1,3,4-thiadiazin-5-ones by the reaction of **2** with mercaptoacetic acid and 2-mercaptopropionic acid [6], and we found that by a two-step synthesis with anthranilic acid 1,4-dihydro-1,3,4-benzotriazepin-5-ones are easily prepared [7]. Some examples of similar monocyclic triazepines, 3-amino-1,2,4-triazepin-5-ones with antifungal and antibacterial properties [8], and some thioxo analogues with interesting properties [9, 10] were described. Here we report about the reaction of **2** with β-alanine yielding 1*H*-1,2,4-triazepin-7-ones **4**, an isomeric structure, which is, to the best of our knowledge, not described until today.

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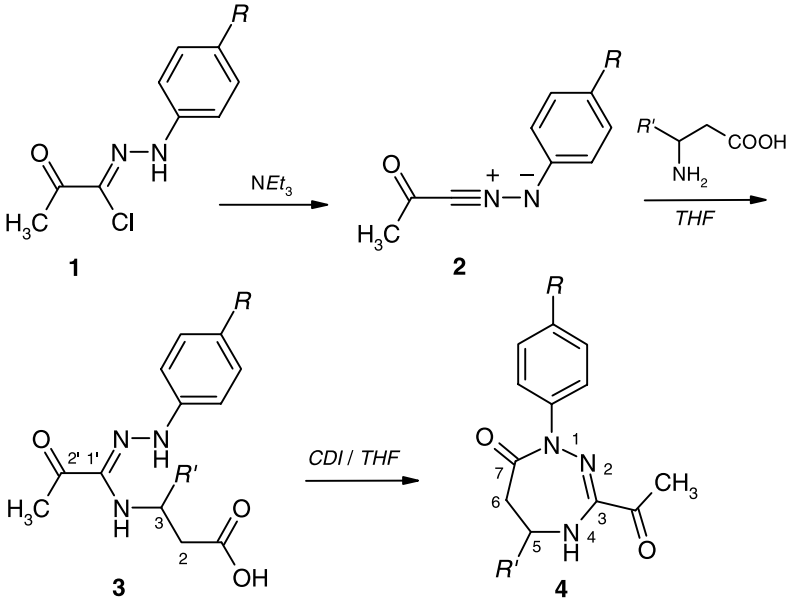
Results and Discussion

The nitrilimines **2a**–**2c** were prepared *in situ* from the hydrazonyl chlorides **1a**–**1c** [11] by reaction with triethylamine, and immediately reacted with β-alanine yielding the corresponding crystalline amidrazones **3a**–**3c** with yields of 60–80%. Their structure was established by ^{1}H and ^{13}C NMR spectroscopy (Fig. 1). In a subsequent step, the acyclic amidrazones **3a**–**3c** in *THF* in the presence of the coupling reagent 1,1′-carbonyldiimidazole underwent facile cyclocondensation involving



a *R*=H **b** *R*=CH_3 **c** *R*=Cl **a-c** *R'*=H *CDI* = 1,1'-carbonyldiimidazole

Scheme 1

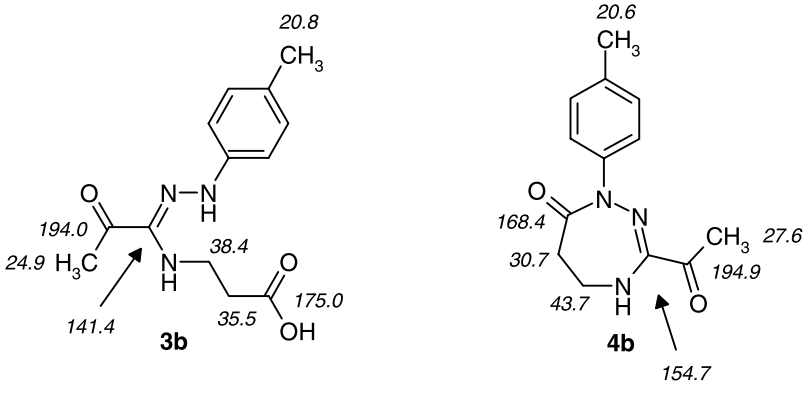


Fig. 1. ^{13}C NMR data of the amidrazone **3b** and the triazepine **4b**

the activated carboxyl group and the hydrazone-NH terminus to deliver the tetrahydro-1*H*-1,2,4-triazepin-7-ones **4a**–**4c**.

The IR, MS, and NMR spectral data and microanalyses of the new compounds **3a**–**3c** and **4a**–**4c** are compatible with the suggested structures; details are given in the experimental section. Thus, their MS spectra display the correct molecular ions suggested by their molecular formulas, and for which the measured high resolution data are in good agreement with the calculated values. ^{1}H signal assignments are straightforward, and ^{13}C assignments follow from DEPT and 2D (COSY, HMQC and HMBC) experiments. Fig. 1 compares the ^{13}C NMR data of **3b** and **4b**.

Experimental

Melting points: Electrothermal Mel. Temp. Apparatus. Elemental analyses: Perkin Elmer elemental analyzer 2400 CHN. Microanalyses were performed at the Microanalytical Laboratory, Inorganic Chemistry Department, Tübingen Universität, Germany; the results agreed with the calculated values within experimental error. IR spectra (KBr): Perkin Elmer Nicolet 205 IR spectrometer. ^{1}H and ^{13}C NMR spectra: Bruker DPX 300 (300 MHz/75 MHz) at room temp., *TMS* as internal standard, $\delta_{TMS} = 0.00$ ppm. Electron-impact mass spectra were obtained using a Finnigan MAT TSQ-70 spectrometer at 70 eV; ion source temperature = 200°C. β-Alanine and 1,1′-carbonyldiimidazole were purchased from Acros. Solvents were purified and dried according to literature procedures. Abbreviations: *Me*OH = methanol, *THF* = tetrahydrofuran, *ar* = aromatic.

General Procedure for the Synthesis of ***3***

To a cooled (0°C) and stirred solution of **1** (10 mmol) in 30 cm^3 of *THF* a solution of β-alanine (1.1 g, 12 mmol) in 20 cm^3 of *Me*OH/H_2O (4:1) and 4 cm^3 of triethylamine were added dropwise. If necessary, additional triethylamine and *Me*OH/H_2O was added to obtain a clear solution, which was stirred at 0°C for 30 min, and then at room temp. for 1–2 h. Then, the organic solvents were distilled off *in vacuo*, and the remaining aqueous solution was immediately acidified with glacial acetic acid (~4 cm^3). The precipitate was separated, washed with 2 × 5 cm^3 of H_2O, dried, and recrystallized from $CHCl_3$/*Me*OH (5:1, *v*/*v*).

3-[2-Oxo-1-(phenylhydrazono)propylamino]propionic acid (**3a**, $C_{12}H_{15}N_3O_3$)

Yield 1.5 g (61%); mp 154–155°C; IR: $\bar{\nu} = 3470$ (NH, OH), 1716, 1673 (CO) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.35$ (s, CH_3), 2.46 (br.t, $J = 7.1$ Hz, 2-H, 2-H), 3.25 (m, 3-H, 3-H), 5.27 (br.s, N–H), 6.78, 7.14–7.24 (2m, 5H, *ar* H), 9.52 [s, N–H(Ph)], 12.43 (s, COOH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 25.0$ (CH_3), 35.6 (C-2), 38.6 (C-3), 113.5, 120.3, 129.2, 145.4 (ar C), 141.8 (C-1′), 174.8 (COOH), 194.2 (C-2′) ppm; MS-EI: m/z (%) = 249 (M^+, 33), 188 (3), 150 (5), 146 (6), 118 (10), 108 (32), 100 (7), 92 (22), 83 (100); HRMS: Calcd. 249.111316, found 249.106711.

3-[2-Oxo-1-(4-methylphenylhydrazono)propylamino]propionic acid (**3b**, $C_{13}H_{17}N_3O_3$)

Yield 2.0 g (76%); mp 167–168°C; IR: $\bar{\nu} = 3454$ (NH, OH), 1717, 1673 (CO) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.21$ (s, CH_3(*ar*)), 2.36 (s, CH_3), 2.49 (m, 2-H, 2-H), 3.22 (m, 3-H, 3-H), 5.22 (br.s, N–H), 7.04, 7.09 (2d, 4H, *ar* H), 9.52 [s, N–H(*ar*)], 12.45 (br.s, COOH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 20.8$ (CH_3(ar)), 24.9 (CH_3), 35.5 (C-2), 38.4 (C-3), 113.5, 129.1, 130.0, 143.1 (*ar* C), 141.4 (C-1′), 175.0 (COOH), 194.0 (C-2′) ppm; MS-EI: m/z (%) = 263 (M^+, 100), 215 (4), 202 (7), 191 (3), 164 (8), 132 (32), 122 (75), 106 (65), 105 (43), 100 (14), 91 (19); HRMS: Calcd: 263.126966, found: 263.126414.

3-[2-Oxo-1-(4-chlorophenylhydrazono)propylamino]propionic acid (**3c**, $C_{12}H_{14}ClN_3O_3$)

Yield 1.9 g (68%); mp 162–163°C; IR: $\bar{\nu} = 3437$ (NH, OH), 1714, 1645 (CO) cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.34$ (s, CH_3), 2.45 (m, 2-H, 2-H), 3.26 (m, 3-H, 3-H), 7.13, 7.24 (2d, 4H, *ar* H), 9.57 (s, N–H(*ar*)), 12.39 (br.s, COOH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 25.2$ (CH_3), 35.6 (C-2), 38.6 (C-3), 114.9, 123.5, 129.4, 144.5 (*ar* C), 142.2 (C-1′), 174.5 (COOH), 194.4 (C-2′) ppm; MS-EI: m/z (%) = 283 (M^+, 79), 222 (26), 184 (14), 180 (7), 154 (10), 142 (92), 126 (80), 100 (59), 43 (100); HRMS: Calcd: 283.07237, found: 283.07125.

General Procedure for the Synthesis of ***4***

1,1′-Carbonyldiimidazole (1.6 g, 10 mmol) was added to a solution of 6 mmol of **3** in 60 cm^3 of *THF*, and the mixture was stirred at room temp. for 1–2 h. The solvent was evaporated *in vacuo*, the residue was treated with 30 cm^3 of H_2O and extracted with 2×30 cm^3 of CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), the solvent was evaporated, and the residue was crystallized from CH_2Cl_2/*n*-hexane.

3-Acetyl-1-phenyl-1,4,5,6-tetrahydro-1H-1,2,4-triazepin-7-one (**4a**, $C_{12}H_{13}N_3O_2$)

Yield 1.0 g (74%); mp 63–65°C; IR: $\bar{\nu} = 3285$ (NH), 1669, 1602 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.32$ (s, CH_3), 2.65 (m, 6-H, 6-H), 3.86 (m, 5-H, 5-H), 6.71 (m, N–H), 6.71–7.22 (m, 5H, *ar* H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 27.5$ (CH_3), 30.6 (C-6), 43.7 (C-5), 113.7, 122.2, 129.4, 146.1 (*ar* C), 154.6 (C-3), 168.4 (C-7), 194.8 (C=O) ppm; MS-EI: m/z (%) = 231 (M^+, 71), 189 (100), 188 (32), 178 (17), 162 (15), 149 (29), 146 (64), 134 (21), 120 (48), 108 (38), 92 (35), 77 (41); HRMS: Calcd: 231.100755, found: 231.099958.

3-Acetyl-1-(4-methylphenyl)-1,4,5,6-tetrahydro-1H-1,2,4-triazepin-7-one
(**4b**, $C_{13}H_{15}N_3O_2$)

Yield 1.6 g (65%); mp 95–96°C; IR: $\bar{\nu} = 3308$ (NH), 1723, 1672 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.22$ (s, CH_3(*ar*)), 2.29 (s, CH_3), 2.69 (t, $J = 7.2$ Hz, 6-H, 6-H), 3.84 (br.t, 5-H, 5-H), 6.49 (br.s, N–H), 6.62, 7.01 (2d, $J = 8.3$ Hz, 4H, *ar* H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 20.6$ (CH_3(*ar*)), 27.6 (CH_3), 30.7 (C-6), 43.7 (C-5), 114.1, 130.0, 131.7, 143.7 (*ar* C), 154.7 (C-3), 168.4 (C-7), 194.9 (C=O) ppm; MS-EI: m/z (%) = 245 (M^+, 78), 203 (100), 202 (24), 176 (17), 160 (59), 148 (22), 134 (54), 121 (31), 106 (45); HRMS: Calcd: 245.116405, found: 245.117320.

3-Acetyl-1-(4-chlorophenyl)-1,4,5,6-tetrahydro-1H-1,2,4-triazepin-7-one
(**4c**, $C_{12}H_{12}ClN_3O_2$)

Yield 1.5 g (57%); mp 142–143°C; IR: $\bar{\nu} = 3285$ (NH), 1671 (CO) cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.32$ (s, CH_3), 2.66 (t, $J = 7.2$ Hz, 6-H, 6-H), 3.86 (m, 5-H, 5-H), 6.52 (br.s, N–H), 6.64, 7.17 (2d, $J = 8.8$ Hz, 4H, *ar* H) ppm; ^{13}C NMR ($CDCl_3$): $\delta = 24.5$ (CH_3), 30.7 (C-6), 43.7 (C-5), 114.8, 127.3, 129.5, 144.7 (*ar* C), 154.1 (C-3), 168.4 (C-7), 194.6 (C=O) ppm; MS-EI: m/z (%) = 265 (M^+, 15), 223 (33), 205 (6), 180 (21), 167 (11), 154 (18), 149 (100), 142 (17), 126 (15), 111 (10); HRMS: Calcd: 265.06181, found: 265.06047.

Acknowledgements

We wish to thank the Deanship of Academic Research, University of Jordan, Amman, Jordan, and the 'Fonds der Chemischen Industrie', Frankfurt, Germany, for financial support. *B.A.T.* thanks the DAAD for a grant.

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