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On the Synthesis of 2-Acetyl-4-aryl-6*H*-1,3,4-thiadiazin-5-ones by Reaction of Nitrilimines with α-Mercapto Alkanoic Acids

Bassam A. Thaher[1] and **Hans-Hartwig Otto**[2,*,a]

[1] Chemistry Department, Islamic University, Gaza, Palestine
[2] Pharmaceutical/Medicinal Chemistry, Institute of Pharmacy, University of Greifswald,
D-17487 Greifswald, Germany

Summary. *N′*-Arylacetonitrilimines were generated from acetohydrazonyl chlorides and reacted with mercaptoalkanoic acids forming 4-aryl-5-oxo-3-thiahexanoic acids. These were cyclized by reaction with dicyclohexyl carbodiimide yielding 2-acetyl-4-aryl-6*H*-1,3,4-thiadiazin-5-ones.

Keywords. Arylacetonitrilimines; 1,3,4-Thiadiazin-5-ones; Cyclization.

Introduction

Nitrilimines like **2** are highly reactive intermediates in heterocyclic syntheses. They allow 1,3-dipolar cycloaddition reactions with multiple bonds [1], cyclocondensation reactions with nucleophilic substrates [2–4], and 1,3-electrophilic additions with nucleophiles [5]. In reactions with α-aminoesters affording 4,5-dihydro-1,2,4-triazin-6-ones [4] and with ethoxycarbonylhydrazine forming 1,3,4-tetrahydro-*s*-triazines [5], acyclic intermediate adducts have been isolated and then cyclized to the corresponding heterocyclic compounds.

We were interested in the question if the reaction between **2** and mercaptoalkanoic acids, which has, to the best of our knowledge, not been described until today, allows the isolation of intermediates or affords 1,3,4-thiadiazin-5-ones in a one-step addition. Furthermore, some similar compounds described in the literature exhibit spasmolytic effects, and some other derivatives have been prepared by known methods to study there biological activity [6–10].

Results and Discussion

The *N*-aryl-substituted acetohydrazonyl chlorides **1** were prepared by a modified literature procedure [4], and the nitrilimines **2** were generated *in situ* from **1** by reaction with triethylamine. The nitrilimines were not isolated, but immediately

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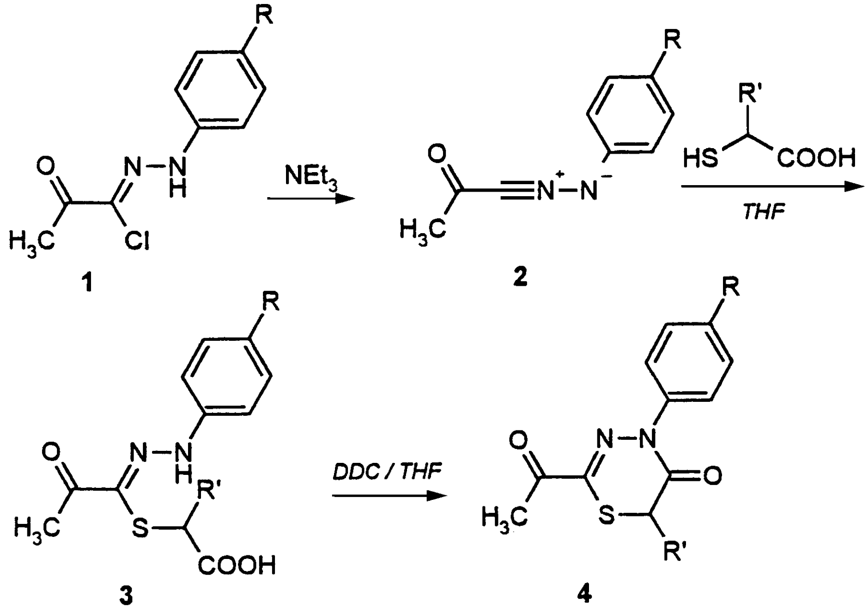
[*] Corresponding author. E-mail: ottohh@pharmazie.uni-greifswald.de

[a] Dedicated to Prof. *Wilhelm Fleischhacker* on the occasion of his 70th birthday

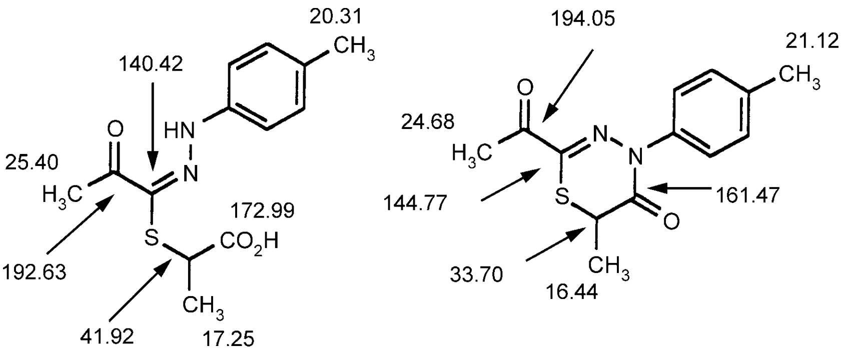
reacted with the mercaptoalkanoic acids. We isolated the corresponding adducts **3** with yields of about 70–80%. All compounds **3** form stable yellow crystals.



3 / 4	a	b	c	d	e	f	g	h
R	H	Cl	Br	CH_3	CH_3	H	Cl	Br
R'	H	H	H	H	CH_3	CH_3	CH_3	CH_3

The IR spectra of **3** are characterized by the NH band around 3236 cm^{-1}, a broad hydroxyl band in the region 3200–2540 cm^{-1} indicating the carboxyl group, a strong and broad carbonyl band around 1720 cm^{-1}, and a C=N band at 1630 cm^{-1}. The ^{1}H NMR spectra show the expected resonance signals of the aliphatic and aromatic protons, especially the singlet of the methyl protons around 2.5 ppm, and for **3a**–**d** a singlet at 3.6–3.7 ppm for the protons at C-2, whereas the corresponding signal in the spectrum of **3e** exhibits a coupling of 7 Hz between the methyl group and the proton at C-2. Furthermore, the signal of the proton at the nitrogen appears as a singlet at 10.7 ppm.

Cyclization was possible either after isolation of **3** or in a one pot procedure by reaction with dicyclohexyl carbodiimide (*DCC*) in tetrahydrofuran at room temperature. The resulting 1,3,4-thiadiazine-5-ones **4** were isolated as stable crystalline products with yields between 85 and 95%. Their structure was confirmed by elemental analyses and spectroscopic data. The IR spectra support the formation of the cyclic structure by the absence of NH and OH bands. In addition, there is an upfield shift of the carbonyl bands of about 20 to 30 cm^{-1}. In contrast to the ^{1}H NMR spectra of **3**, those of **4** are characterized by the absence of exchangeable protons. The protons of the acetyl group in position 2 resonate at about 2.5 ppm,



3e **4e**

Fig. 1. ^{13}C NMR data of **3e** and **4e** ($CDCl_3$, room temperature)

whereas the signals of the protons at C-6 of **4a**–**d** are found as singlets around 3.5 ppm, showing an upfield shift of 0.1 ppm as compared to the spectra of **3**. In the NMR spectra of **4e**–**h**, the methyl protons at C-6 are found as doublets with $J = 7$ Hz at *ca.* 1.6 ppm, whereas the proton at C-6 is registered as a quartet at ~3.7 ppm. Finally, the structures are corroborated by their ^{13}C NMR data (Fig. 1).

There is a pronounced upfield shift of about 13 ppm of the signal of the carboxylic group at *ca.* 170 ppm in the acyclic adducts **3** in comparison to its position in **4** where it is found as an amide signal at 157–162 ppm. Furthermore, the signal of the methylene carbon of the thioacetic acid moiety in **3** at about 33.5 ppm is shifted upfield in **4a**–**d** (~26.4 ppm), whereas the signal of C-6 in **4e**–**h** is registered at *ca.* 33.7 ppm.

In conclusion, the results demonstrate that the reaction between nitrilimines and mercaptoalkanoic acids is a clear two-step reaction.

Experimental

Melting points: Linström apparatus (uncorrected); IR spectra (KBr): Perkin Elmer FTIR 1600; NMR spectra: Bruker ARX 200 (^{1}H: 200 MHz, ^{13}C: 50 MHz), room temperature, internal *TMS*, $CDCl_3$ if not noted otherwise; elemental analyses: Perkin Elmer elemental analyzer 2400 CHN; the results agreed with the calculated values within experimental error. Mercaptoacetic acid and 2-mercaptopropanoic acid were purchased from Merck, Darmstadt. Solvents were purified and dried according to literature procedures. Abbreviations: *DCC* = dicyclohexyl carbodiimide, EtOAc = ethyl acetate, EtOH = ethanol, *THF* = tetrahydrofuran, arom. = aromatic.

Synthesis of 4 *(general procedure)*

a) Reaction of nitrilimines with mercaptoacetic acid: Triethylamine (5.0 g, 0.05 mol) in 10 cm^3 *THF* was added dropwise to a stirred solution of 0.01 mol hydrazonyl chloride and 4.6 g mercaptoacetic acid (0.05 mol) in 40 cm^3 *THF* at room temperature, and stirring was continued for 6 days; then the solvent was evaporated *in vacuo*. The residue was partitioned between EtOAc and H_2O. The aqueous layer was extracted with EtOAc (2 × 30 cm^3), and the combined organic layers were extracted with saturated $NaHCO_3$ solution (3 × 30 cm^3). The combined extracts were cooled to 0°C, acidified with conc. HCl, and extracted with EtOAc (3 × 30 cm^3). The combined EtOAc extracts were washed with 30 cm^3 brine, dried (Na_2SO_4), and evaporated. The residue was either treated with EtOH, whereby **3** could be isolated by slow evaporation, or immediately cyclized to **4**.

b) *Cyclization*: The residue from *a*) or isolated **3** was dissolved in 30 cm^3 *THF*, and a solution of 1 equiv. *DCC* in 10 cm^3 *THF* was added. The mixture was stirred for 1–2 h at room temperature, the precipitate (dicyclohexyl urea) was filtered off, and the filtrate was evaporated *in vacuo*. The viscous residue was dissolved in EtOH, and by slow evaporation of the solvent **4** was obtained.

2-Acetyl-4-phenyl-6H-1,3,4-thiadiazin-5-one (**4a**; $C_{11}H_{10}N_2O_2S$)

a) *5-Oxo-4-(phenylhydrazono)-3-thiahexanoic acid* (**3a**; $C_{11}H_{12}N_2O_3S$): Yield: 69%; yellow crystals; m.p.: 142–143°C (*THF*/petroleum ether); IR: $\nu = 3238$ (NH), 3200–2542 (OH), 3016, 2971, 2917 (CH), 1723 (CO), 1628 (C=N), 1226 (C–S), 1171 (C–O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.42$ (s, 3H, CH_3), 3.66 (s, 2H, CH_2), 7.0–7.5 (m, 5H, arom. H) ppm.

b) **4a**: yield: 85%; pale yellow crystals; m.p.: 57–58°C (EtOH); IR: $\nu = 3067$, 2984, 2929 (CH), 1690 (CO), 1207 (C–S), 1138 (C–O) cm^{-1}; ^{1}H NMR: $\delta = 2.50$ (s, 3H, CH_3), 3.56 (s, 2H, CH_2), 7.47–7.26 (m, 5H, arom. H) ppm; ^{13}C NMR: $\delta = 24.69$ (CH_3), 26.39 (CH_2), 125.19, 127.79, 128.84, 140.80 (arom. C), 145.98 (C=N), 157.62 (C-5), 193.61 (CO) ppm.

2-Acetyl-4-(4-chlorophenyl)-6H-1,3,4-thiadiazin-5-one (**4b**; $C_{11}H_9ClN_2O_2S$)

a) *4-(4-Chlorophenylhydrazono)-5-oxo-3-thiahexanoic acid* (**3b**; $C_{11}H_{11}ClN_2O_3S$): Yield: 86%; yellow crystals; m.p.: 145–146°C (EtOH); IR: $\nu = 3236$ (NH), 3230–2549 (OH), 3000, 2964, 2960 (CH), 1720 (CO), 1634 (C=N), 1228 (C–S), 1169 (C–O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.42$ (s, 3H, CH_3), 3.68 (s, 2H, CH_2), 7.48–7.35 (m, 4H, arom. H), 10.70 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 25.49$ (CH_3), 33.52 (CH_2), 116.15, 125.89, 128.98, 133.15 (arom. C), 141.87 (C=N), 170.41 (COOH), 192.66 (CO) ppm.

b) **4b**: yield: 93%; colorless needles; m.p.: 120–121°C (EtOH); IR: $\nu = 3005$, 2924 (CH), 1702, 1682 (CO), 1205 (C–S), 1132 (C–O) cm^{-1}; ^{1}H NMR: $\delta = 2.50$ (s, 3H, CH_3), 3.56 (s, 2H, CH_2), 7.53–7.33 (m, 4H, arom. H) ppm; ^{13}C NMR: $\delta = 24.73$ (CH_3), 26.43 (CH_2), 126.37, 129.01, 133.46, 139.13 (arom. C), 146.56 (C=N), 157.59 (C-5), 193.49 (CO) ppm.

Acetyl-4-(4-bromophenyl)-6H-1,3,4-thiadiazin-5-one (**4c**; $C_{11}H_9BrN_2O_2S$)

a) *4-(4-Bromophenylhydrazono)-5-oxo-3-thiahexanoic acid* (**3c**; $C_{11}H_{11}BrN_2O_3S$): Yield: 73%; yellow crystals; m.p.: 144–145°C (EtOH); IR: $\nu = 3237$ (NH), 3230–2533 (OH), 2974, 2970 (CH), 1720 (CO), 1635 (C=N), 1226 (C–S), 1170 (C–O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.51$ (s, 3H, CH_3), 3.69 (s, 2H, CH_2), 7.53–7.37 (m, 4H, arom. H), 10.67 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d_6): $\delta = 25.51$ (C-6), 33.53 (C-2), 113.85, 116.62, 131.83, 133.30 (arom. C), 142.30 (C-4), 170.42 (C-1), 192.64 (C-5) ppm.

b) **4c**: yield: 85%; colorless needles; m.p.: 125–126°C (EtOH); IR: $\nu = 3002$, 2923 (CH), 1705, 1681 (CO), 1630 (C=N), 1219 (C–S), 1131 (C–O) cm^{-1}; ^{1}H NMR: $\delta = 2.50$ (s, 3H, CH_3), 3.55 (s, 2H, CH_2), 7.60–7.35 (m, 4H, arom. H) ppm; ^{13}C NMR: $\delta = 24.67$ (CH_3), 26.45 (CH_2), 121.41, 126.64, 131.99, 139.69 (arom. C), 146.62 (C=N), 157.50 (C-5), 193.33 (CO) ppm.

2-Acetyl-4-(4-methylphenyl)-6H-1,3,4-thiadiazin-5-one (**4d**; $C_{12}H_{12}N_2O_2S$)

a) *4-(4-Methylphenylhydrazono)-5-oxo-3-thiahexanoic acid* (**3d**; $C_{12}H_{14}N_2O_3S$): Yield: 72%; yellow crystals; m.p.: 143–144°C (EtOH); IR: $\nu = 3235$ (NH), 3200–2564 (H), 2973, 2920 (CH), 1741, 1708 (CO), 1619 (C=N), 240 (C–S), 1193 (C–O) cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.26$ (s, 3H, CH_3), 2.48 (s, 3H, CH_3), 3.64 (s, 2H, CH_2), 7.36–7.12 (m, 4H, arom. H), 10.52 (s, 1H, NH) ppm; ^{13}C NMR

(*DMSO*-d$_6$): $\delta = 20.28$ (CH$_3$), 25.38 (C-6), 33.65 (C-2), 114.67, 129.56, 131.44 (arom. C), 140.48 (C-4), 170.60 (C-1), 192.49 (C-5) ppm.

b) **4d**: yield: 86%; pale yellow crystals; m.p.: 93–94°C (EtOH); IR: $\nu = 3001$, 2926, 2850 (CH), 1684 (CO), 1627 (C=N), 1208 (C–S), 1145 (C–O) cm^{-1}; ^{1}H NMR: $\delta = 2.40$ (s, 3H, CH$_3$) 2.50 (s, 3H, CH$_3$), 3.55 (s, 2H, CH$_2$), 7.35–7.23 (m, 4H, arom. H) ppm; ^{13}C NMR: $\delta = 21.13$ (CH$_3$), 24.72 (CH$_3$), 26.41 (CH$_2$), 126.12, 129.51, 137.9, 138.27 (arom. C), 145.72 (C=N), 157.58 (C-5), 193.77 (CO) ppm.

(RS)-2-Acetyl-6-methyl-4-(4-methylphenyl)-6H-1,3,4-thiadiazin-5-one (**4e**; $C_{13}H_{14}N_2O_2S$)

a) (RS)-2-Methyl-4-(4-methylphenylhydrazono)-5-oxo-3-thiahexanoic acid (**3e**; $C_{13}H_{16}N_2O_3S$): Yield: 79%; yellow crystals; m.p.: 144–145°C (EtOH); IR: $\nu = 3235$ (NH), 3153–2560 (OH), 3016, 2971, 2917 (CH), 1709, 1692 (CO), 1628 (C=N), 1237 (C–S), 1200 (C–O) cm^{-1}; ^{1}H NMR (*DMSO*-d$_6$): $\delta = 2.26$ (s, 3H, CH$_3$), 2.48 (s, 3H, CH$_3$), 3.64 (s, 2H, CH$_2$), 7.36–7.12 (m, 4H, arom. H), 10.52 (s, 1H, NH) ppm; ^{13}C NMR (*DMSO*-d$_6$): $\delta = 17.25$ ((CH$_3$)–C2), 20.31 (CH$_3$), 25.40 (C-6), 41.92 (C-2), 114.82, 129.54, 130.93, 131.42 (arom. C), 140.42 (C-4), 172.99 (C-1), 192.63 (C-5) ppm.

4e: yield: 86%; pale yellow crystals; m.p.: 95–96°C; IR: $\nu = 2990$, 2926, 2850 (CH), 1688 (CO), 1626 (C=N), 1247 (C–S), 1169 (C–O) cm^{-1}; ^{1}H NMR: $\delta = 1.55$ (d, $J = 7$ Hz, 3H, CH$_3$), 2.40 (s, 3H, CH$_3$), 2.50 (s, 3H, CH$_3$), 3.66 (q, $J = 7$ Hz, 1H, CH), 7.39–7.18 (m, 4H, arom. H) ppm; ^{13}C NMR: $\delta = 16.64$ (CH$_3$), 21.12 (CH$_3$), 24.68 (CH$_3$), 33.70 (CH), 125.16, 129.49, 137.86, 138.68 (arom. C), 144.77 (C=N), 161.47 (C-5), 194.05 (CO) ppm.

(RS)-2-Acetyl-6-methyl-4-phenyl-6H-1,3,4-thiadiazine-5-one (**4f**; $C_{12}H_{12}N_2O_2S$)

Yield: 76%; light-yellow crystals; m.p.: 123–124°C; IR: $\nu = 3002$, 2957 (CH), 1693, 1675 (CO), 1596 (C=N), 1204 (C–S), 1135 (C–O) cm^{-1}; ^{1}H NMR: $\delta = 1.56$ (d, $J = 7$ Hz, 3H, CH$_3$), 2.50 (s, 3H, CH$_3$), 3.67 (q, $J = 7$ Hz, 1H, CH), 7.25–7.55 (m, 5H, arom. H) ppm.

(RS)-2-Acetyl-4-(4-chlorophenyl)-6-methyl-6H-1,3,4-thiadiazine-5-one (**4g**; $C_{12}H_{11}ClN_2O_2S$)

Yield: 83%; light-yellow crystals; m.p.: 100–103°C; IR: $\nu = 2974$, 2927 (CH), 1683 (CO), 1221 (C–S), 1162 (C–O) cm^{-1}; ^{1}H NMR: $\delta = 1.55$ (d, $J = 7$ Hz, 3H, CH$_3$), 2.50 (s, 3H, CH$_3$), 3.66 (q, $J = 7$ Hz, 1H, CH), 7.2 (m, 4H, arom. H) ppm.

(RS)-2-Acetyl-4-(4-bromophenyl)-6-methyl-1,3,4-thiadiazine-5-one (**4h**; $C_{12}H_{11}BrN_2O_2S$)

Yield: 86%; yellow crystals; m.p.: 112–113°C; IR: $\nu = 3064$, 2974, 2930 (CH), 1685 (CO), 1215 (C–S), 1132 (C–O) cm^{-1}; ^{1}H NMR: $\delta = 1.55$ (d, $J = 7$ Hz, 3H, CH$_3$), 2.50 (s, 3H, CH$_3$), 3.66 (q, $J = 7$ Hz, 1H, CH), 7.46 (m, 4H, arom. H) ppm; ^{13}C NMR: $\delta = 16.32$ ((CH$_3$)–C6), 24.72 (CH$_3$), 33.73 (C-6), 121.35, 126.70, 131.97, 140.02 (arom. C), 145.75 (C-2), 161.45 (C-5), 193.78 (CO) ppm.

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