Organic Syntheses Based on 2-Oxoglutaric Acid. V. Syntheses of Novel 2*H*-1,4-Benzothiazines and a 2,5-Dihydro-1,5-benzothiazepine

Torsten Blitzke, Dieter Sicker*, and Horst Wilde

Institut für Organische Chemie der Universität Leipzig, Talstr. 35, D-04103 Leipzig, Germany

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Syntheses aimed on the incorporation in heterocycles of segments originating in the precursor 2-oxoglutaric acid are described. Cylocondensation of dimethyl 2-oxoglutarate **1**, dimethyl 3-bromo-2-oxoglutarate **2**, and dimethyl (*E*)-2-oxoglutaconate **3** with 2-aminobenzenethiol gave rise to the novel 2*H*-1,4-benzothiazines **4** and **5**, and the 2,5-dihydro-1,5-benzothiazepine **6**, respectively, by incorporation of either the segments C-1/C-2 or C-2/C-3 or C-3/C-4/C-5 of the precursor.

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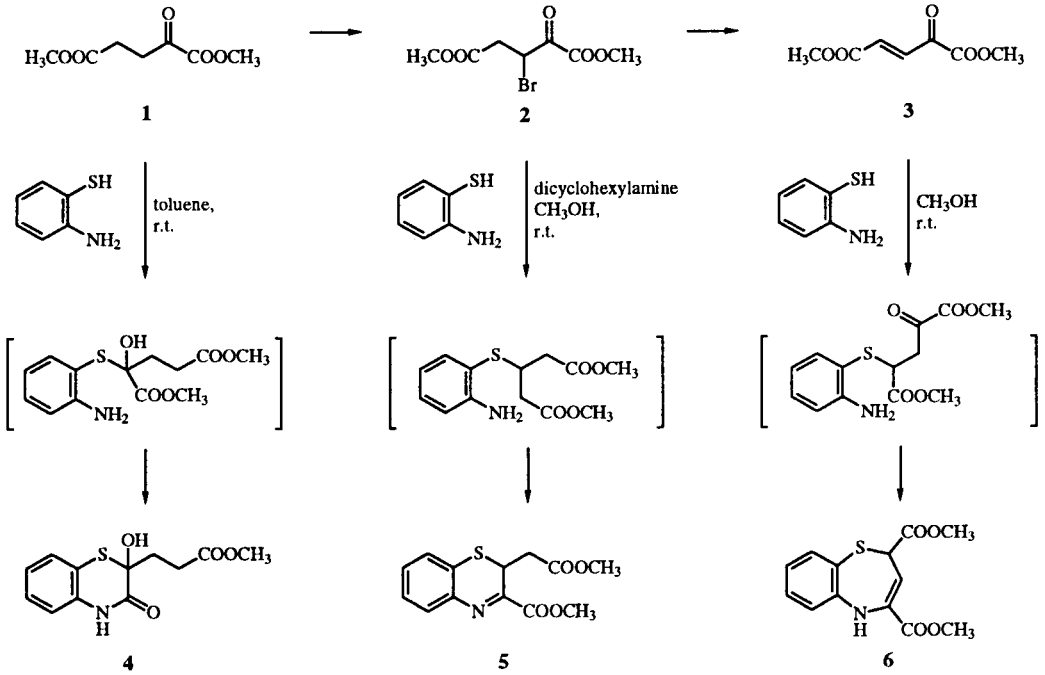
2-Oxoglutaric acid is a well known constituent of metabolism. However, its availability for the synthetic chemist was for a long time limited due to the expensive chemical synthesis [1]. However, during the last decade fermentation of *n*-paraffines with the yeast *Yarrowia lipolytica* was shown to offer a convenient biotechnological access [2]. In this text, we have reported on possibilities to use synthetical dimethyl 2-oxoglutarate **1** [3] and dimethyl 3-bromo-2-oxoglutarate **2** [4]. Furthermore, the transformation of the latter ester into dimethyl (*E*)-2-oxoglutaconate **3** has been reported [5,6]. 2-Oxoalkene **3** has been shown to be a useful building block for heterocycles [6,7], *e.g.* for the natural product 4,5-dihydro-4,5-dioxo-1*H*-pyrrolo[2,3-*f*]quinoline-2,7,9-tricarboxylic acid [8], the organic redox cofactor of quinoproteines.

Based on this work we wish to report here on the transformation of the esters **1**, **2**, and **3** into novel heterocycles by reaction with 2-aminobenzenethiol as the binucleophile.

Results and Discussion.

Dimethyl 2-oxoglutarate **1** is known to cyclize with heteroanalogous binucleophiles like 1,2-phenylenediamines and 2-aminophenol to form quinoxalin-2(1*H*)-ones [9] and a 2*H*-1,4-benzoxazin-2-one derivative [10], respectively. In both cases, the reaction is initiated by the attack of an amino group as the strongest nucleophile at the 2-C=O group in **1** leading to an intermediate azomethine, which undergoes a cyclocondensation by reaction of the second nucleophile with the 1-$COOCH_3$ unit. However, in 2-aminobenzenethiol the SH-group is the strongest nucleophile. Therefore, the cyclocondensation with **1** at room temperature in toluene leads to methyl 3-(2-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-on-2-yl)-propionate **4** *via* an intermediate hemimercaptal as a result of the initial addition of the thiophenol unit to the 2-oxo group. Because this hemimercaptal does not undergo elimination of water, an interesting tertiary alcohol unit



1 **2** **3**

4 **5** **6**

remains in **4**. Recently, we have described a synthesis for the closely related cyclic hemimercaptal 2-hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-one [11], the thio analogue of the natural product *Blepharigenin* [12] from *Gramineae*. Many structurally related 1,4-benzothiazines have been reported to be of pharmacological interest [13].

As we have shown, dimethyl 3-bromo-2-oxoglutarate **2** reacts with an 1,3-*S*,*N*-binucleophile, *e.g.* thiocarbohydrazide, with incorporation of the C-3/C-2 segment into the heterocycle formed [4]. Analogously, **2** reacted like an α-halogeno ketone with 2-aminobenzenethiol as 1,4-*S*,*N*-binucleophile and gave rise to methyl 2-(3-methoxy-carbonyl-2*H*-1,4-benzothiazin-2-yl)acetate **5**. The reaction is expected to proceed *via* an intermediate thioether arising from the initial nucleophilic substitution of the activated halogen function in **2**. The yield obtained is only moderate. However, a feature of **2** is its sensitivity towards elimination of hydrogen bromide in the presence of a base to yield alkene **3**. Therefore, the relation between nucleophilic and basic strength of the binucleophile used is of importance in order to suppress the elimination. We have found a means to enhance the nucleophilicity of 2-aminobenzenethiol by reacting it in the presence of an equimolar amount of dicyclohexylamine, which causes formation of the 2-aminobenzenethiolate anion.

Dimethyl (*E*)-2-oxoglutaconate **3** was shown to cyclize as an α-ketoester with 1,2-phenylenediamine [6] and 2-aminophenols [14] leaving the olefinic unit unaffected. In contrast, **3** reacted as a vinologous ketone with 2-aminobenzenethiol to form dimethyl (2,5-dihydro-1,5-benzothiazepin-2,4-diyl)dicarboxylate **6**. A plausible mechanism for this reaction consists in an attack of the thiol at the electrophilic C-4 in **3**, followed by cyclization of the amine with the 2-C=O group of the intermediate. Recently, a series of 1,5-benzothiazepine derivatives of pharmaceutical interest has been described [15] and we have reported on a synthesis for the dehydro analogue of **6** [16].

In summary, the segments C-1/C-2, C-2/C-3 and C-3/C-4/C-5 of 2-oxoglutaric acid have been incorporated by cyclocondensation of its derivatives **1**, **2**, and **3** with 2-aminobenzenethiol into the novel heterocycles **4**, **5**, and **6**, respectively.

EXPERIMENTAL

Melting points were determined on a Boetius micro hot-stage apparatus and are corrected. Elemental analyses were performed on a Heraeus CHN-O-Rapid analyzer. The nmr spectra were recorded on a Varian Unity 400 spectrometer at 399.952 MHz for ^{1}H and at 100.577 MHz for ^{13}C with hexamethyldisiloxane as the internal standard. The ir spectra were obtained on a Carl Zeiss Jena Specord M 80 spectrometer in potassium bromide. Mass spectra were recorded on a Finnigan MAT 212 spectrometer (70 eV EI ionisation, source temperature 200°). The following educts were prepared according to the literature: dimethyl 2-oxoglutarate (**1**) [3], dimethyl 3-bromo-2-oxoglutarate (**2**) [4], and dimethyl (*E*)-2-oxoglutaconate (**3**) [6].

Methyl 3-(2-Hydroxy-2*H*-1,4-benzothiazin-3(4*H*)-on-2-yl)propionate (**4**).

A solution of **1** (3.48 g, 20 mmoles) in toluene (10 ml) was dropwise added to a solution of 2-aminobenzenethiol (2.51 g, 20 mmoles) in toluene (20 ml) and stirred for 3 hours at room temperature. The crude product precipitated was filtered off, washed with toluene and recrystallized from toluene to yield 2.68 g (50%) of **4** as colourless needles, mp 157-159°; ir: ν 3293, 3202, 1729, 1647 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.10-2.35 (m, 2H, CH_2), 2.50-2.75 (m, 2H, CH_2-COO), 3.62 (s, 3H, OCH_3), 4.93 (s, 1H, OH), 6.90-7.30 (m, 4H, aromatics), 9.58 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 28.4 (CH_2), 31.9 (CH_2), 51.7 (OCH_3), 77.0 (C-2') 117.4 (C-5'), 119.9 (C-8a'), 123.6 (C-8'), 127.1 (C-7'), 127.9 (C-6'), 136.0 (C-4a'); 167.3 (C-3'), 173.6 (C-1); ms: m/z 267 (M^+, 10), 249 (10), 237 (30), 190 (65), 152 (100).

Anal. Calcd. for $C_{12}H_{13}NO_4S$: C, 53.92; H, 4.90; N, 5.24. Found: C, 53.55; H, 4.93; N, 5.12.

Methyl 2-(3-Methoxycarbonyl-2*H*-1,4-benzothiazin-2-yl)acetate (**5**).

Dicyclohexylamine (1.81 g, 10 mmoles) was dropwise added to a solution of 2-aminobenzenethiol (1.26 g, 10 mmoles) in absolute methanol (30 ml) with stirring at 20° under a nitrogen atmosphere. After 10 minutes a solution of **2** (2.53 g, 10 mmoles) in absolute methanol was added dropwise. After 2 additional hours of stirring the bromide formed was filtered off, the solvent removed *in vacuo* and the remaining residue extracted with n-hexane (4 x 80 ml). Crystallization of the extract yielded 1.2 g (43%) of yellow crystals of **5**, mp 84-85°; ir: ν 1740, 1718, 1430, 1240 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.47 (dd, 1H, 2a-H, $^3J_{2a\text{-}H/2'\text{-}H}$ = 8.8 Hz, $^2J_{2a\text{-}H/2b\text{-}H}$ = 16.1 Hz), 2.57 (dd, 1H, 2b-H, $^3J_{2b\text{-}H/2'\text{-}H}$ = 6.2 Hz, $^2J_{2a\text{-}H/2b\text{-}H}$ = 16.1 Hz), 3.67 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 4.65 (dd, 1H, 2'-H, $^3J_{2a\text{-}H/2'\text{-}H}$ = 8.8 Hz, $^3J_{2b\text{-}H/2'\text{-}H}$ = 6.2 Hz), 7.24-7.65 (m, 4H, aromatics); ^{13}C nmr (deuteriochloroform): δ 29.4 (C-2'), 35.1 (C-2), 52.1 (OCH_3), 53.6 (OCH_3), 121.8 (C-3'), 127.0, 128.3, 129.72, 129.73 (C-5', C-6', C-7', C-8'), 140.9 (C-8a'), 149.5 (C-4a'), 164.1 (COO), 170.0 (COO); ms: m/z 279 (M^+, 100), 246 (3), 219 (75), 206 (48), 191 (81), 160 (53).

Anal. Calcd. for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.01. Found: C, 55.99; H, 4.71; N, 5.38.

Dimethyl (2,5-Dihydro-1,5-benzothiazepin-2,4-diyl)dicarboxylate (**6**).

A solution of **3** (1.72 g, 10 mmoles) in absolute methanol (5 ml) was added to a solution of 2-aminobenzenethiol (1.26 g, 10 mmoles) in methanol (10 ml) and stirred for 20 hours. The precipitate formed was filtered off and recrystallized twice from methanol to yield 1.4 g (50%) of **6** as colourless needles, mp 142-143°; ir: 3350, 1728, 1712 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 3.63 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 4.41 (d, 1H, 2-H, J = 7.0 Hz), 6.28 (d, 1H, 3-H, J = 7.0 Hz), 6.90-7.40 (m, 4H, aromatics), 7.42 (s, 1H, NH); ^{13}C nmr (deuteriochloroform): δ 48.3 (C-2), 52.8 (OCH_3), 53.4 (s, 3H, OCH_3), 105.8 (C-3), 120.9 (C-6), 122.2 (C-9a), 122.3 (C-9), 129.4 (C-8), 130.7 (C-5a), 134.8 (C-7), 146.0 (C-4), 165.9 (COO), 169.5 (COO); ms: m/z 279 (M^+, 10), 220 (100), 188 (70), 160 (29).

Anal. Calcd. for $C_{13}H_{13}NO_4S$: C, 55.90; H, 4.69; N, 5.01. Found: C, 55.78; H, 4.80; N, 4.97.

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