Ring Transformation and Cyclization Reactions of 1,1-Dioxo-1,2-thiazines – Syntheses of Pyridines and Benzo[*c*]thiazines with New Substitution Pattern

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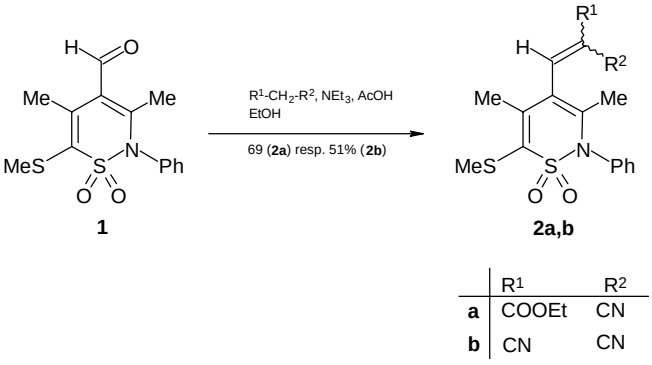
Abstract. In presence of ammonia/ammonium acetate the 3,5-dimethyl-2-phenyl-1,1-dioxo-1,2-thiazine-4-carbaldehyde (**1**) reacts with ethyl cyanoacetate to the ethyl 2-cyano-4-[1-methyl-2-methylthio-2-(*N*-phenylsulfamoyl)vinyl)-hexa-2,4-dienoate (**3**) and the Knoevenagel condensation product 4-(2-ethoxycarbonyl-2-cyanovinyl)-3,5-dimethyl-6-methylthio-1,1-dioxo-2-phenyl-2*H*-1,2-thiazine (**2**a). The 4-(2,2-dicyanovinyl)-3,5-dimethyl-6-methylthio-1,1-dioxo-2-phenyl-2*H*-1,2-thiazine (**2b**) is obtained from **1** and malononitril. The masked 1,5-dicarbonyl compound **2a** undergoes rind transformation to the 3-cyano-1,6-dimethyl-5-[1-methylthio-2-(*N*-phenylsulfamoyl)vinyl]pyridin-2-one (**5**) with methylamine. With ethanolic ethoxide the condensation products **2a,b** afford the 7-amino-6-ethoxycarbonyl-4-methylthio-2,2-dioxo-1-phenyl-benzo[c]1,2-thiazine (**6a**), respectively the corresponding 6-cyano derivative **6b**, while **3** cyclizises to furnish ethyl 2-amino-6-methyl-5-[1-methyl-2-methylthio-2-(*N*-phenyl-sulfamoyl)vinyl]nicotinate (**4**)

In former papers we described the synthesis [1] and the reactions of 1,1-dioxo-1,2-thiazine-6-carbaldehydes [2]. These compounds react as masked 1,5-dicarbonyl compounds with ammonia or amines under ring transformation to pyridines. The related thiazine-4-carbaldehydes – as masked 1,3-dicarbonyl compounds – give with nitrogen 1,2- or 1,3-dinucleophiles like hydrazines or amidines *N*-arylsulfamoylvinyl substituted pyrazoles or pyrimidines [3, 4]. In this paper we describe Knoevenagel condensations of the 1,1-dioxo-1,2-thiazine-4-carbaldehyde **1** with ethyl cyanoacetate and malononitrile. The products contain a masked 1,5-dicarbonyl structure and should yield pyridines by ring transformation with amines.

The 1,1-dioxo-1,2-thiazine-4-carbaldehyde **1** reacts with ethyl cyanoacetate or malononitrile in the presence of triethylamine and acetic acid at room temperature to yield the condensation products **2a**,**b**. Under these reaction conditions no reaction was observed with the less C-H-acidic acetylacetone (Scheme 1).

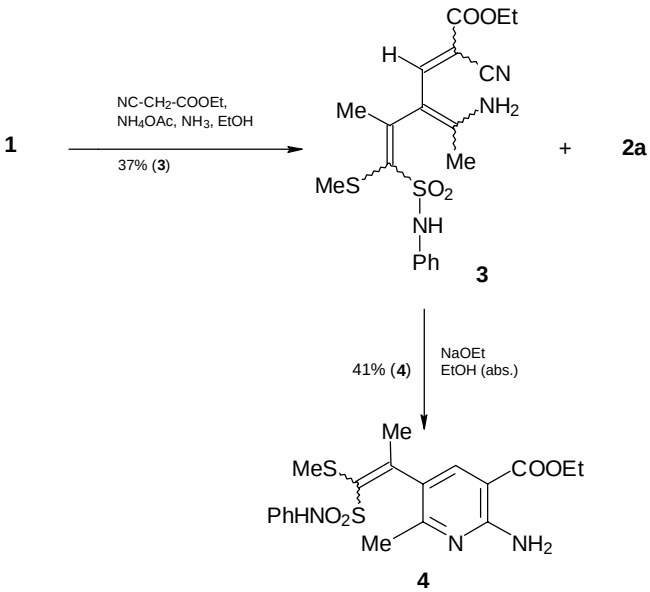


	R^1	R^2
a	COOEt	CN
b	CN	CN

Scheme 1

In the presence of ammonium acetate and ammonia the reaction of the carbaldehyde **1** with ethyl cyanoacetate in ethanol a beige solid was obtained in 37% yield together with the Knoevenagel product **2a** (11%). The main product was characterized by NMR as the open-chain compound **3**. It should be formed *via* a nucleophilic attack of ammonia on the 3-position of the thiazine ring in **1** or **2a** (Scheme 2).

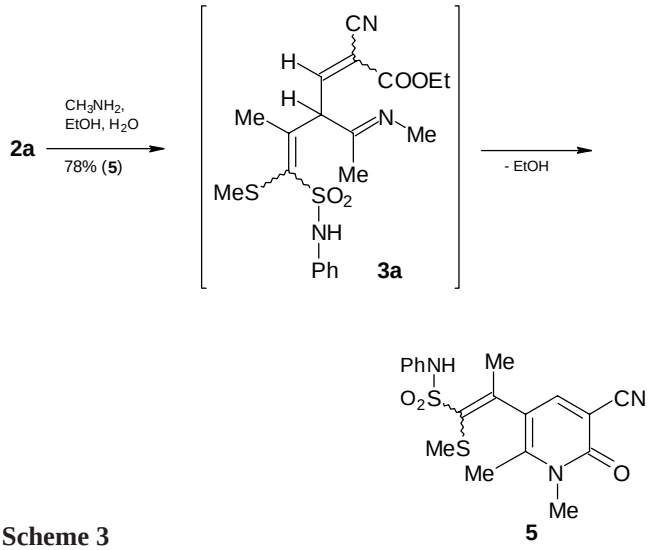
The substituted 2-amino nicotinate **4** is easily synthesised from **3** by a sodium ethanolate induced ring closure reaction at room temperature.



Scheme 2

  1436-9966/99/3410X-403 $ 17.50 + .50/0

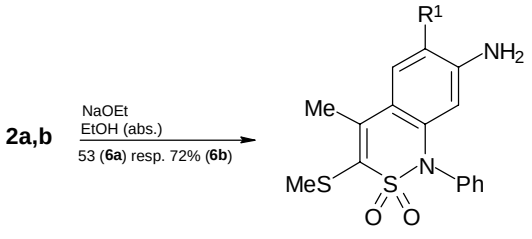
Ring transformation of **2a** with methylamine gives the 2-pyridone **5,** probably by a mechanism similar to that described for the ring transformation of the thiazine-4-carbaldehydes with hydrazines [3]. A 1,5-Michael addition of the amine to the masked $\alpha,\beta,\gamma,\delta$-unsaturated carbonyl compound **2a** (attack on the 3-position of the 1,1-dioxo-1,2-thiazine ring) is followed by ring opening to the intermediate **3a** which closes the ring by reaction of the enamine/imine group with the ester group (Scheme 3).This selective ring closure is favoured under the used week basic reaction conditions, while a strong basic medium induces the cyclization *via* the cyano group (see **4** and **6ab**).



Scheme 3

Related 3-cyanopyridin-2-ones are of pharmaceutical interest ("Milrinon") [5, 6]. Furthermore, they are versatile starting materials for syntheses of the cardiologic active imidazo- and thiazolo[4,5-*b*]pyridin-2-(3*H*)-ones, which are presently intensively investigated [7, 8].

We reported previously that the C-H acidic 3-methyl group of 1,1-dioxo-1,2-thiazines is easily attacked by electrophiles [9]. An example is the mild thiolation of **1** by sulfur in the presence of triethylamine to give a thieno[3,4-*c*][1,2]thiazine [10]. Correspondingly, the 3-methyl group of the Knoevenagel products **2a**,**b** is deprotonated with sodium ethanolate.



	R^1
a	COOEt
b	CN

Scheme 4

The resulting intermediate attacks the nitrile group to yield the benzo[*c*]thiazines **6a**,**b**. This is a convenient method for the preparation of substituted 2,2-dioxo-benzo[*c*]1,2-thiazines (Scheme 4).

The structures of all new compounds were elucidated by their NMR spectra (see Experimental).

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Experimental

NMR spectra were measured using a Varian Gemini 300 spectrometer (^{1}H NMR 300 MHz; ^{13}C NMR 75 MHz) and TMS as internal standard. IR spectra were recorded on a Philips PU 9426 FTIR spectrometer as KBr pellets and MS (EI) spectra using an AMD 402 spectrometer. Microanalyses were performed on a Leco CHNS-932 analyzer. Satisfactory microanalyses were obtained for all new substances (C, H, N, S, ± 0,4%). The 3,5-dimethyl-6-methylthio-1,1-dioxo-2-phenyl-1,2-thiazine-4-carbaldehyde (**1**) was synthesized as described in the literature [3].

4-(2-Ethoxycarbonyl-2-cyanovinyl)-3,5-dimethyl-6-methylthio-1,1-dioxo-2-phenyl-2H-1,2-thiazine (**2a**)

To a suspension of **1** (100 mg, 0.323 mmol) in EtOH (5 ml) ethyl cyanoacetate (0.035 ml, 0.328 mmol), Et_3N (0.045 ml, 0.323 mmol) and one drop of AcOH were added. After stirring for 24 h 90% of the solvent was removed *in vacuo*. The product **2a** was separated as a yellow solid. Yield 91mg (69%); *m.p.* 144 °C. – IR: ν/cm^{-1} = 2227 (CN), 1727 (CO) and 1596. – ^{1}H NMR (DMSO-d_6): δ/ppm = 1.29 (3H, t, 7 Hz, CH_3), 1.99, 2.37, 2.43 (3H, s, 3CH_3), 4.30 (2H, q, 7 Hz, CH_2), 7.32 (2H, m, ArH), 7.56 (3H, m, ArH), 8.34 (1H, s). – ^{13}C NMR (DMSO-d_6): δ/ppm = 14.1, 19.4, 19.5, 19.6, 62.6, 110.0, 113.9, 114.9, 118.5, 128.9, 129.7, 130.2, 134.4, 146.9, 148.5, 156.5 and 161.3. – MS: *m/z* (%) = 404 (M^+, 71), 340 (31), 325 (100).

4-(2,2-Dicyanovinyl)-3,5-dimethyl-6-methylthio-1,1-dioxo-2-phenyl-2H-1,2-thiazine (**2b**)

To a suspension of **1** (100 mg, 0.323 mmol) in EtOH (5 ml) malononitrile (21 mg, 0.32 mmol), Et_3N (5 µl, 0.0323 mmol) and one drop of AcOH were added. After stirring for 3 h 90% of the solvent was removed *in vacuo*. The product **2b** was separated as a yellow solid. Yield 59 mg (51); *m.p.* 186–189 °C (EtOH). IR: ν/cm^{-1} = 2229 (CN). – ^{1}H NMR (DMSO-d_6): δ/ppm = 2.03, 2.35, 2.44 (3H, s, 3CH_3), 7.32 (2H, m, ArH), 7.56 (3H, m, ArH), 8.56 (1H, s). – ^{13}C NMR (DMSO-d_6): δ/ppm = 19.4, 19.6,87.4, 112.8, 113.5, 113.7, 123.0, 129.6, 130.1, 130.4, 133.9, 148.3, 149.1, 159.9. – MS: *m/z* (%) = 357 (M^+), 293 (19), 278 (85), 263 (36).

Ethyl 2-cyano-4-[1-methyl-2-methylthio-2-(N-phenylsulfamoyl)vinyl]hexa-2,4-dienoate (**3**)

To a suspension of **1** (100 mg, 0.323 mmol) in EtOH (5 ml) NH_4OAc (38 mg, 0.493 mmol), ethyl cyanoacetate (0.035 ml, 0.328 mmol) and ammonia liquor (22%, 0.04 ml,

≈ 0.5 mmol) were added. After stirring for 72 h 90 % of the solvent was removed *in vacuo*. The precipitated solid was washed with water and recrystallized from ethanol to yield **3**. From the filtrate the solvent was removed *in vacuo* to yield the side product **2a**. Yield 45 mg (37%); *m.p*. 187–188 °C (EtOH). IR: ν/cm^{-1} = 2192 (CN), 1689 (CO). – ^{1}H NMR (DMSO-d$_6$): δ/ppm = 1.21 (3H, t, 6.7 Hz, CH_3), 2.19, 2.29, 2.35 (3H, s, 3CH_3), 4.10 (2H, q, 5 Hz, CH_2), 6.94 (2H, m, ArH), 7.14 (3H, m, ArH), 7.35 (1H, br s), 7.72 (1H, br s), 8.40 (1H, br s), 9.8 (1H, br s). – ^{13}C-NMR (DMSO-d$_6$): δ/ppm = 14.7, 17.5, 18.6, 26.6, 59.9, 78.2, 108.4, 118.4, 119.1, 122.5, 128.8, 138.7, 138.9, 147.4, 152.8, 164.3, 166.4. – MS: *m/z* (%) = 421 (M$^+$,71), 404 (100), 340 (34), 325 (93).

Ethyl 2-Amino-6-methyl-5-[1-methyl-2-methylthio-2-(N-phenyl-sufamoyl)vinyl]nicotinate (**4**)

To a suspension of **3** (100 mg, 0,237 mmol) in abs. EtOH (5 ml) a solution of sodium ethanolate (3.5 mg Na, 0.152 mmol, 2 ml abs. EtOH) was added. After stirring for 24 h the solvent was removed *in vacuo*. The residue was suspended in water to yield **4** as a light yellow solid. Yield 40 mg (41%); *m.p*. 221–223 °C (EtOH). – IR: ν/cm^{-1} = 1685 (CO). – ^{1}H NMR (DMSO-d$_6$): δ/ppm = 1.31 (3H, t, 6.8 Hz, CH_3), 2.09 (3H, s, CH_3), 2.33 (6H, s, CH_3), 4.28 (2H, q, 6.8 Hz, CH_2), 7.01 (3H, m, ArH), 7.14 (2H, s, NH_2), 7.23 (3H, m, ArH), 7.41 (1H, s, C(4)H), 10.1 (1H, s, NH). – ^{13}C NMR (DMSO-d$_6$): δ/ppm = 14.4, 19.0, 22.3, 27.1, 60.6, 101.8, 119.4, 123.6, 124.2, 129.1, 134.6, 136.9, 137.9, 157.6, 158.3, 166.6. – MS: *m/z* (%) = 421 (M$^+$, 54), 265 (54), 218 (100).

3-Cyano-1,6-dimethyl-5-[1-methyl-2-methylthio-2-(N-phenylsulfamoyl)vinyl]pyridin-2-one (**5**)

Route A: To a suspension of **2a** (100 mg, 0,247 mmol) in EtOH (5 ml) a solution of methylamine in water (0.031 ml, 0.333 mmol, 33%) was added. After stirring for 24 h 50% of the solvent was removed *in vacuo*, and the precipitated pyridin-2-one **5** was separated. Yield 75mg, (78%); *m.p*. 237–240 °C (EtOH). IR: ν/cm^{-1} = 2229 (CN), 1637 (CO). – ^{1}H NMR (DMSO-d$_6$): δ/ppm = 2.10, 2.29, 2.38 (3H, s, 3CH_3), 3.47 (3H, s, NCH_3), 7.00 (3H, d, 7.8 Hz, ArH), 7.08 (1H, t, 7.3 Hz, ArH), 7.28 (2H, t, 7.4 Hz, ArH), 7.35 (1H, s, C(4)H), 9.8 (1H, br s, NH). – ^{13}C NMR (DMSO-d$_6$): δ/ppm = 18.8, 19.0, 26.5, 32.0, 98.4, 116.8, 117.9, 120.2, 124.1, 129.3, 137.4, 137.6, 145.3, 151.0, 153.9, 159.9. – MS: *m/z* (%) = 389 (M$^+$, 30), 233 (19), 186 (100).

Route B: To a suspension of **1** (100 mg, 0.323 mmol) in EtOH (5 ml) NH_4OAc (38 mg, 0.493 mmol), ethyl cyanoacetate (0.035 ml, 0.328 mmol) and a solution of methylamine in water (33%, 0.03 ml, ≈ 0.323 mmol) were added. After stirring for 72 h 50% of the solvent was removed *in vacuo* and **5** separated. Yield 15 mg (12%); *m.p*. 237–240 °C (EtOH).

7-Amino-6-ethoxycarbonyl-4-methyl-3-methylthio-2,2-dioxo-1-phenyl-benzo[c]-1,2-thiazine (**6a**)

To a suspension of **2a** (100 mg, 0,247 mmol) in abs. EtOH (1 ml) a solution of sodium ethanolate (6.25 mg Na, 0.272 mmol, 1ml abs. EtOH) was added. After stirring for 24 h water (10 ml) was added and **6a** separated as a white solid by centrifugation. Yield 53 mg (53%); *m.p*. 151–152 °C (EtOH). IR: ν/cm^{-1} = 1695 (CO), 1313, 1153. – ^{1}H NMR (DMSO-d$_6$): δ/ppm = 1.31 (3H, t, 6.5 Hz, CH_3), 2.37, 2.63 (3H, s, 2CH_3), 4.28 (2H, q, 6.6 Hz , CH_2), 5.95 (1H, s, C(8)H), 7.16 (2H, s, NH_2), 7.34 (2H, m, ArH), 7.56 (3H, m, ArH), 8.15 (1H, s, C(5)H). – ^{13}C NMR (DMSO-d$_6$): δ/ppm = 14.4, 18.3, 20.0, 60.5, 104.0, 106.2, 111.7, 123.7, 129.5, 129.7, 130.4, 132.4, 135.5, 145.4, 148.9, 152.9, 166.6. – MS: *m/z* (%) 404 (M$^+$, 100), 325 (80).

7-Amino-6-cyano-4-methyl-3-methylthio-2,2-dioxo-1-phenyl-benzo[c]-1,2-thiazine (**6b**)

To a suspension of **2b** (100 mg, 0,28 mmol) in abs. EtOH (1 ml) a solution of sodium ethanolate (7 mg Na, 0.3 mmol, 0.2 ml abs. EtOH) was added. After stirring for 4 h **6b** was separated as a white solid. Yield 72 mg (72%); *m.p*. 189 – 191 °C. – IR: ν/cm^{-1} = 1322, 1151. – ^{1}H NMR (DMSO-d$_6$): δ/ppm 2.37, 2.63 (3H, s, 2CH_3), 5.94 (1H, s, C(8)H), 6.67 (2H, s, NH_2), 7.3 (2H, d, 7 Hz, ArH), 7.56 (3H, m, ArH), 7.96 (1H, s, C(5)H). – ^{13}C NMR (DMSO-d$_6$): δ/ppm = 19.1, 20.6, 91.5, 103.5, 113.3, 118.0, 125.0, 130.8, 131.1, 131.4, 135.5, 136.1, 146.1, 149.2, 153.6. – MS: *m/z* (%) = 357 (M$^+$, 98), 278 (100).

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