Ring Transformation of 1,1-Dioxo-1,2-thiazine-6-carbaldehydes with Nitrogen Nucleophiles to Substituted Pyridine-3-sulfonanilides

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1,1-Dioxo-1,2-thiazine-6-carbaldehydes I possessing a masked 1,5-dicarbonyl structure react with hydroxylamine with ring transformation to form the pyridine N-oxides 2. These can be deoxygenated with PCl₃ to give the corresponding pyridine-3-sulfonanilides 3, which are available by the reaction of 1 with ammonia as well. The ring transformation of 1 with methylation, benzylamine and hydrazine produces N-substituted mesoionic pyridinium salts 6-8. The cyclohexane-fused thiazine-6-carbaldehyde 9 can be transformed with ammonia to the 5,6,7,8-tetrahydroquinoline 10. Reaction of 2 with NaNO₂/HCl enables the introduction of the nitro group into the amide part of the molecule.

Ring transformations are competitive synthetic principles for the structural modification of heterocyclic compounds. In six-membered heterocycles with one heteroatom ring transformations generally start by the nucleophilic attack of suitable bases on a heterocyclic salt. The new and more stable cyclic system is formed by ring opening followed by ring closure. Examples are the conversion of pyrylium salts into benzenes or pyridines by keeping up the ring size or the transformation of pyrimidinium-3-diazonium salts into β-(1,2,3-triazol-4-yl)acroleins under ring contraction. The SO₂-extrusion to pyroles as well as the nitrosoating cleavage of the cyclic sulfonamide structure to mesoionic pyrazidinium salts are known as ring transformations of 1,1-dioxo-1,2-thiazines.

In this paper we describe the synthetic potential of 2-aryl-1,1-dioxo-1,2-thiazine-6-carbaldehydes I as masked, unsaturated 1,5-dicarbonyl compounds, which react with nitrogen nucleophiles in a one-pot reaction to produce the so far unknown substituted pyridine-3-sulfonanilide derivatives. In order to check the generalization of this new type of ring transformation, we changed the substituent in the aryl group of the 2-aryl-1,1-dioxo-1,2-thiazine-6-carbaldehydes 1 from a donor (OCH₃, CH₃) into a weak acceptor substituent (Cl). By changing the nitrogen nucleophiles, pyridines and pyridine N-oxides are available, as well as mesoionic N-alkyl and N-aminopyridinium salts.

The pharmacological significance of pyridine derivatives and the easy accessibility of 1,1-dioxo-1,2-thiazines are reasons for studying this new synthetic pathway for substituted pyridine-3-sulfonanilides (2,4-lutidine-5-sulfonanilides), which are normally obtainable only by a multistep synthesis.

1,1-Dioxo-1,2-thiazine-6-carbaldehydes I are synthesized by Vilsmeier-Haack formylation of the 2-aryl-3,5-dimethyl-1,1-dioxo-1,2-thiazines. The aldehydes react with hydroxylamine to produce high melting compounds, which were characterized as pyridine N-oxides by means of spectroscopic data and chemical reactions. The N-oxides are deoxygenated with PCl₃ to give the corresponding pyridines. Until now it has not been decided whether the first step of the reaction of I with hydroxylamine is the formation of an aldoxime or the ring opening to an aldo-ketoxime.

Reaction of 2b with NaNO₂/hydrochloric acid affords a well crystallizing compound 4b from which monocrystals could be grown. The X-ray crystallographic analysis of 4b (Figure) and the ¹H NMR data confirm the transformation of 1b to the pyridine N-oxide 2b and the nitration of the sulfanilide part of the molecule. The MS data of 4b additionally verify that a nitro group and not a nitroso substutent is introduced into the molecule.

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Scheme 1

Scheme 2
nitrosation of 2a results in the formation of the mono-
(4a) and dinitro-substituted (5a) anilidosulfonfyl pyridine
N-oxide which depends on the ratio of 2a: NaNO₂.
The position of the nitro group in 4 and 5a was de-
termined by NMR spectroscopic data and the calculation of the chemical shift by increments. A significant
ortho-directing effect of the NH₂SO₃ structural element
can be observed. Similar nitrations with NaNO₂/acetic
acid are described for aryl sulfonanilides (see Ref. 18).

Figure. Molecular Structure of 4b

The ring transformation of 1 with hydroxylamine could
be generalized. The aldehydes 1 react with ammonia to
produce the pyridines 3, which are accessible also from
the pyridine N-oxides 2 (Tables 1,2). The transformation
of the aldehydes 1 into the corresponding N-methyl-, N-
benzyl- and N-aminopyridinium salts 6-8 proceeds by
reaction with methylene, benzylamine and hydrazine,
respectively, in ethanol. These mesoionic compounds are
salt-like in their behavior and show the absence of a
counterion.

The ring transformation fails when the basicity of the nitrogen nucleophile is low and the reaction medium
is acidic. The aldehyde 1b reacts with semicarbazide
hydrochloride to give its semicarbazone as evident by
¹H NMR spectroscopic data. The chemical shift of the
ring proton H-4 (δ = 6.02) in the obtained semicarbazone
of 1b corresponds to the shifts observed for 1,1-dioxo-1,2-
thiazines (δ = 6.1). The protons of the pyridine deri-

Ring transformations of both the 6-acyl-substituted
1,1-dioxo-1,2-thiazines and 1,1-dioxo-1,2-thiazine-4-
and 5-carbaldehydes are under investigation.

NMR spectra were measured using a Varian Gemini 300 spectrometer (¹H NMR 300 MHz, ¹³C NMR 75 MHz). The NMR data
are gathered in Tables 1-4. IR spectra were recorded on a Philips
PU 9426 FTIR spectrometer as KBr (Fluka Chemical Co.) pellets. Mass spectra (EI) were obtained using an AMD 402 spectrometer.
Microanalyses were performed on a Leco CHNS-932 analyser.
Satisfactory microanalyses were obtained for all new substances
(C, H, N, O ± 0.5%).

5-Anilidosulfonfyl-2,4-dimethylpyridine N-Oxides 2, General Procedure:
The appropriate aldehyde 1b* (1.8 mmol) was suspended in EtOH
(10 mL), and a solution of NH₃·H₂O·HCl (188 mg, 2.7 mmol) and
Na₂CO₃ (268 mg, 2.7 mmol) in water (6 mL) was added. The mixture
was heated under reflux for 1 h. After cooling, the alcohol was
removed under vacuum and the aqueous solution was mixed with
water (15 mL). The insoluble solid was filtered and the filtrate
was neutralized with dil HCl. The precipitate was isolated by suction,
washed with water (2 × 5 mL), dried and recrystallized from EtOH
(Table 1).

5-Anilidosulfonfyl-2,4-dimethylpyridines 3; General Procedure:
Method A: The appropriate pyridine N-oxide 2 (0.33 mmol) was suspended in CHCl₃ (5 mL), and PCl₃ (200 µL, 2.3 mmol) was
added. The mixture was heated under reflux for 1 h. The mixture
was filtered and the filtrate extracted, after addition of CHCl₃
(10 mL), with aq 10% Na₂CO₃ solution (3 × 5 mL). The aqueous
layers were neutralized by adding 2 M HCl and were extracted with
CHCl₃ (3 × 5 mL). The combined organic layers were dried
(MgSO₄) and concentrated under vacuum to 3 mL. The resulting
solution was mixed with hexane (10 mL) and the precipitated 3
was separated by suction and dried.
Method B: The appropriate aldehyde 1 (0.18 mmol) was suspended in
EtOH (5 mL). Then concentrated NH₄OH (10 mL) was added. The mixture was stirred at r.t. for 24 h. The reaction can be followed by the dissolution of the aldehyde. Evaporation of the solvent at
reduced pressure provided 3 (Table 2).

2,4-Dimethyl-5-[(nitrophenylamido)sulfonyl]pyridine N-Oxides 4a, b
and 5a; General Procedure:
The pyridine N-oxide 2a or 2b (1 mmol) was dissolved in a mixture
of MeCN (7 mL) and conc HCl (0.25 mL). A solution of NaNO₂
in water (amounts see below) was added dropwise over 1 h to the
iced and stirred mixture. The flask was stored at r.t. for 3 d. The reaction can be monitored by TLC (silica gel, cyclohexane/CH₂Cl₂:1:1). The aqueous layer was separated and the organic layer was
Table 1. Compounds 2a–d Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>IR (KBr) (cm⁻¹)</th>
<th>δ, J (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>64</td>
<td>224–226</td>
<td>1155, 1246, 1335, 1508</td>
<td>2:3, 2.43 (s, 3H, Py-CH₃), 3.69 (s, 3H, OCH₂), 6.86, 7.02 (d, 2H, J = 8.9, Ar-H), 7.53, 8.28 (s, 1H, Py-H), 10.4 (s, 1H, NH)</td>
</tr>
<tr>
<td>2b</td>
<td>59</td>
<td>202–203</td>
<td>1151, 1250, 1338, 1510</td>
<td>2.17 (s, 3H, Ar-CH₃), 2.29, 2.44 (s, 3H, Py-CH₃), 6.99, 7.07 (d, 2H, J = 8.9, Ar-H), 7.48, 8.36 (s, 1H, Py-H), 10.6 (s, 1H, NH)</td>
</tr>
<tr>
<td>2c</td>
<td>57</td>
<td>234–236</td>
<td>1149, 1250, 1348, 1498</td>
<td>2.29, 2.44 (s, 3H, Py-CH₃), 7.07–7.3 (m, 5H, Ar-H), 7.51, 8.39 (s, 1H, Py-H), 10.74 (s, 1H, NH)</td>
</tr>
<tr>
<td>2d</td>
<td>80</td>
<td>248–250</td>
<td>1153, 1248, 1329, 1489</td>
<td>2.30, 2.44 (s, 3H, Py-CH₃), 7.12, 7.35 (d, 2H, J = 8.7, Ar-H), 7.52, 8.41 (s, 1H, Py-H), 10.91 (s, 1H, NH)</td>
</tr>
</tbody>
</table>

*¹³C NMR (DMSO-d₆/TMS): δ = 17.1, 18.3 (Py-CH₃), 20.5 (Ar-CH₃), 121.0 (Ar-C₂), 130.1 (Ar-C₃), 130.1 (Py-C₆), 133.7 (Ar-C₄), 133.9 (Py-C₂), 134.4 (Py-C₄), 134.9 (Ar-C₁), 137.9 (Py-C₃), 151.7 (Py-C₅).

Table 2. Compounds 3a–d Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield* (%)</th>
<th>mp (°C)</th>
<th>MS (70 eV) (m/z) (%)</th>
<th>IR (KBr) (cm⁻¹)</th>
<th>δ, J (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>60 (70)</td>
<td>148–150</td>
<td>292 (M⁺, 100)</td>
<td>1153, 1326, 1508, 1597</td>
<td>2.41, 2.48 (s, 3H, Py-CH₃), 3.62 (s, 3H, OCH₂), 6.74, 6.91 (d, 2H, J = 8.8, Ar-H), 7.21, 8.6 (s, 1H, Py-H), 10.3 (s, weak, NH)</td>
</tr>
<tr>
<td>3b</td>
<td>69 (85)</td>
<td>186–188</td>
<td>276 (M⁺, 40)</td>
<td>1161, 1336, 1508, 1608</td>
<td>2.17 (s, 3H, Ar-CH₃), 2.44, 2.53 (s, 3H, Py-CH₃), 6.98, 7.04 (d, 2H, J = 8.4, Ar-H), 7.25, 8.71 (s, 1H, Py-H), 10.36 (s, 1H, NH)</td>
</tr>
<tr>
<td>3c</td>
<td>44</td>
<td>201–203</td>
<td>262 (M⁺, 100)</td>
<td>1153, 1342, 1491, 1601</td>
<td>2.44, 2.53 (s, 3H, Py-CH₃), 6.98–7.24 (m, 5H, Ar-H), 7.32, 8.76 (s, 1H, Py-H), 10.56 (s, 1H, NH)</td>
</tr>
<tr>
<td>3d</td>
<td>45 (70)</td>
<td>180–181</td>
<td>296 (M⁺, 100)</td>
<td>1153, 1333, 1493, 1599</td>
<td>2.43, 2.51 (s, 3H, Py-CH₃), 7.08, 7.29 (d, 2H, J = 8.6, Ar-H), 7.28, 8.73 (s, 1H, Py-H), 10.69 (s, 1H, NH)</td>
</tr>
</tbody>
</table>

* Yields given in parenthesis refer to Method B (see experimental).

Table 3. Compounds 4a, b and 5 Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>mp (°C)</th>
<th>MS (70 eV) (M⁺, 100) m/z (%)</th>
<th>IR (KBr) (cm⁻¹)</th>
<th>δ, J (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>65</td>
<td>194–196.5</td>
<td>353</td>
<td>1151, 1240, 1338, 1538</td>
<td>17.1, 18.5 (Py-CH₃), 56.3 (OCH₂), 110.2 (Ar-C₃), 119.8 (Ar-C₅), 120.3 (Ar-C₁), 130.1 (Py-C₆), 131.3 (Ar-C₆), 134.1 (Py-C₂), 135.2 (Py-C₄), 137.4 (Py-C₃), 147.2 (Py-C₅), 151.8 (Ar-C₅), 158.5 (Ar-C₄)</td>
</tr>
<tr>
<td>4b</td>
<td>55</td>
<td>202–203.5</td>
<td>337</td>
<td>1155, 1236, 1342, 1543</td>
<td>17.0, 18.4 (Py-CH₃), 20.2 (Ar-CH₃), 125.4 (Ar-C₆), 125.8 (Ar-C₁), 128.6 (Ar-C₃), 128.8 (Ar-C₅), 134.1 (Py-C₂), 134.8 (Ar-C₄), 135.3 (Py-C₄), 137.4 (Py-C₃), 138.6 (Ar-C₄), 145.1 (Ar-C₂), 151.8 (Py-C₅), 158.4 (Ar-C₅)</td>
</tr>
<tr>
<td>5a</td>
<td>47</td>
<td>243–245</td>
<td>398</td>
<td>1153, 1242, 1346, 1546</td>
<td>17.1, 18.4 (Py-CH₃), 57.3 (OCH₂), 113.3 (Ar-C₁), 114.5 (Ar-C₃), 130.2 (Py-C₆), 134.4 (Py-C₂), 135.5 (Py-C₄), 157.0 (Py-C₃), 150.5 (Ar-C₅), 151.9 (Py-C₅), 159.2 (Ar-C₄)</td>
</tr>
</tbody>
</table>

│ ¹³C NMR (DMSO-d₆/TMS): δ |

1 > 2α(I). Diffraction: Stoe STADI 4. The computation and drawings were performed by using the programs SHELXS-86, SHELXL-93 and XP/PC.¹¹

*N-Methyl-2,4-dimethylpyridinium-5-sulfonanilides 6; General Procedure:
The appropriate aldehyde 1 (0.11 mmol) was suspended in EtOH (5 mL). Then a solution of MeNH₂·HCl (15 mg, 0.22 mmol) and Na₂CO₃ (35 mg, 0.33 mmol) in water (4 mL) was added. After stirring for 6 h, the solvent was evaporated, then the residue was washed with Et₂O (10 mL) and the product dissolved in CHCl₃ (10 mL) and precipitated by adding Et₂O. The product was isolated by suction and dried.

concentrated under reduced pressure and mixed with diethyl ether (5 mL). After crystallization, the product was filtered and dried. Amounts of NaN₃ used in the preparation of 4a, b and 5:

4a: 1 mmol (69 mg) NaN₃ in 0.2 mL H₂O. 4b: 2 mmol (138 mg) NaN₃ in 0.6 mL H₂O. 5a: 2.5 mmol (173 mg) NaN₃ in 0.7 mL H₂O.

X-ray Investigation of 4b²⁹

C₅H₇N₂O₂S M₀ = 337.35, monoclinic, space group P2₁/c, a = 8.120(1), b = 10.802(2), c = 17.409(3), β = 90.57(1)³, V = 1496.0(4) Å³, Z = 4, F(000) = 704, MoKα radiation (λ = 0.71073 Å). The structure was solved by direct methods of phase determination and refined by full-matrix-least-squares techniques on F², wR₂ = 0.1069 (3303 reflections), R₁ = 0.0377 (2342 reflections with 1 > 2α(I)). Diffraction: Stoe STADI 4. The computation and drawings were performed by using the programs SHELXS-86, SHELXL-93 and XP/PC.¹¹
N-Benzyl-2,4-dimethylpyridinium-5-sulfonanilides 7; General Procedure:
The appropriate aldehyde $I$ (0.11 mmol) was suspended in EtOH (5 mL). Then Et$_3$N (0.03 mL, 0.22 mmol) and benzylamine (0.03 mL, 0.22 mmol) were added and the mixture was stirred for 3 h. The solvent was evaporated to a volume of 2 mL and the product was precipitated by adding EtOH. It was isolated by suction and dried.

N-Amino-2,4-dimethylpyridinium-5-sulfonanilides 8; General Procedure:
The appropriate aldehyde $I$ (0.11 mmol) was suspended in EtOH (5 mL). Then water (0.12 mL) and $N_2$H$_4$·$H_2$O (0.01 mL, 0.22 mmol) were added. The mixture was stirred for 3 h. After evaporating the solvent and washing the residue with Et$_2$O (5 mL) and several times with CHCl$_3$ (3 mL), 8 was obtained analytically pure (Table 4).

4,7-Dimethyl-1,1-dioxo-2-phenyl-1,2-(3,4,5,6-tetrahydrobenzo)[c]thiazine-9-carboxaldehyde (9):
TiCl$_4$ (1.65 mL, 15 mmol) and dichloromethyl methyl ether$^{22}$ (0.93 mL, 10 mmol) were added at 0°C to a stirred suspension of 4,7-dimethyl-1,1-dioxo-2-phenyl-1,2-(3,4,5,6-tetrahydrobenzo)[c]thiazin (Pulegoultsulame)$^{13}$ (1.44 g, 5 mmol) in CH$_2$Cl$_2$ (15 mL).
The stirring was continued at 0°C for 1 h and the mixture was kept at r.t. for 24 h. The mixture was poured into ice water (20 mL) and stirred for 1 h. The organic phase was separated, washed with water, the organic layer was concentrated at reduced pressure and then to the residue hexane was added. The precipitate was isolated by suction and dried. The crude product was purified by column chromatography (silica gel, EtOAc), yield: 355 mg (21%); mp 170–174°C.

$^1$H NMR (CDCl$_3$/TMS): $\delta = 0.89$ (d, 3H, $J = 6.5$ Hz, CH$_3$)$_2$, 2.56 (s, 3H, CH$_3$)$_2$, 1.2–2.5 (m, 7H), 7.36–7.44 (m, 5H, Ar–H), 9.84 (s, 1H, CHO).

$^{13}$C NMR (CDCl$_3$/TMS): $\delta = 16.4, 20.9, 25.4, 28.0, 29.8, 37.9, 117.5, 122.3, 129.1, 129.5, 129.7, 133.9, 148.4, 156.2, 182.7 (CHO).

3-Amidobisulfonfyl-4,7-dimethyl-5,6,7,8-tetrahydroquinoline (10):
The quinoline 10 was synthesized analogically to the preparation of the pyridines 3 (method B) from the aldehyde 9 (317 mg, 1 mmol), EtOH (7 mL) and conc. $NH_4OH$ (4 mL); yield: 224 mg (71%); mp 196–197°C (EtOH).

$^1$H NMR (DMSO-d$_6$/TMS): $\delta = 1.06$ (d, 3H, $J = 6.4$ Hz, CH$_3$)$_2$, 2.44 (s, 3H, CH$_3$)$_2$, 1.3–2.6 (m, 7H), 7.03–7.24 (m, 5H, Ar–H), 8.82 (s, 1H, Py–H), 10.5 (s, 1H, NH).

IR (KBr): $v = 1153, 1343, 1489, 1573$ cm$^{-1}$.

3,4-Dimethyl-2-(4-methylphenyl)-1,1-dioxo-2,3-thiazine-6-carboxaldehyde Semicarbazone:
The aldehyde 1b (50 mg, 0.18 mmol) was suspended in EtOH (5 mL), water (1 mL) and conc. HCl was added until the pH reached 2. Semicarbazide hydrochloride (40 mg, 0.36 mmol) was added to this solution, the mixture was stirred for 3 h and the product isolated by suction. The semicarbazone of 1b was obtained analytically pure; yield: 48 mg (80%); mp 219–220°C (EtOH).

$^1$H NMR (DMSO-d$_6$/TMS): $\delta = 1.90$ (s, 3H, Ar–CH$_3$), 2.31 (s, 3H, CH$_3$)$_2$, 2.40 (s, 3H, CH$_3$)$_2$, 6.02 (s, 1H), 6.28 (s, NH$_2$), 7.21–7.36 (m, 4H, Ar–H), 7.83 (s, 1H, CH), 10.39 (s, 1H, NH).

IR (KBr): $v = 771, 1390, 1689, 1951$ cm$^{-1}$.

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(20) Further details of the crystal structure determination are available on request from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, D-76344 Eggenstein-Leopoldshafen, or quoting the depository number CSD-404766.
Sheldrick, G. M.; SHELXL-93, Program for the refinement of crystal structures, Univ. Göttingen, Germany (1993).