Synthesis of Substituted Phenyl 2-Aminopyridine-3-sulfonates

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Abstract: A series of phenyl 2-aminopyridine-3-sulfonates 3 has been synthesized starting from phenyl cyanomethanesulfonate (5). Pinner reaction with 5 gave phenoxysulfonylketene aminal 4K which was cycl condensed with a series of C₂-biselectrophiles to yield the title compounds, which are of pharmaceutical and medicinal interest.

Key words: pyridines, condensation, tautomerisation, phenoxysulfonylketene aminals, 2-aminopyridine-3-sulfonates

Pyrido-1,2,4-thiadiazine-1,1-dioxides e.g. 2 become more significant as selective potassium channel openers and aza-isosters of diazoxide (1), an antihypertensive agent.1–5

As part of our research program on the rational synthesis of functionalized and anellated pyridines we report the convenient preparation of 2-aminopyridine-3-sulfonates 3 (R = Ph) which, after ammonolysis to 2-aminopyridine-3-sulfonamides, should serve as starting material for medicinal interesting pyrido[2,3-e][1,2,4]thiadiazine-1,1-dioxides 2 (R¹ = Ar, Alk, Hal; R² = H, Me). A short retrosynthetic view will explain our approach (Scheme 1). Title compounds 3 were considered to be prepared by an C₁–C₂N-pyridine synthesis6–9 via diprimary phenoxysulfonylketene aminal 4K, which could be generated from the key starting material phenyl cyanomethanesulfonate (5).

Krutak et al.10 reported the synthesis of 5, without giving experimental details. Phenyl cyanomethanesulfonate (5) can easily be prepared by dehydration of amide 611 with phosphorous oxychloride (Scheme 2).

Following the outlined strategy, phenyl cyanomethanesulfonate (5) was treated, according to Pinner’s procedure, with methanol or ethanol and hydrogen chloride in diethyl ether at 0 °C to yield the imidate hydrochlorides 7a·HCl and 7b·HCl. On refluxing 7a·HCl and 7b·HCl respectively, with ammonium acetate in ethanol deprotonation and ammonolysis of the alkoxy group took place, giving the amidine 4A, which exists in a tautomeric equilibrium with ketene aminal 4K. We found that ketene aminal 4K could not be isolated in a pure state.

The 1,3-bisnucleophile 4K was generated in situ from 7b·HCl and ammonium acetate and cyclocondensed with 1,3-biselectrophiles e.g. β-aminovinylketones 8a–e,g and

![Scheme 1](image1)

![Scheme 2](image2)
The trimethinium salt 9 and bromomalonaldehyde (10) were reacted with 4K yielding the pyridines 3h and 3i (Table 1).

Table 1  Reaction of 1,3-Bis-Electrophiles 3 with Ketene Aminals 4K

<table>
<thead>
<tr>
<th>1,3-Bis-</th>
<th>Product R¹</th>
<th>R²</th>
<th>Yield (%)</th>
<th>Mp  (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nucleophiles</td>
<td>3a</td>
<td>Ph</td>
<td>H</td>
<td>76</td>
</tr>
<tr>
<td>8a</td>
<td>3b</td>
<td>4-MeOPh</td>
<td>H</td>
<td>67</td>
</tr>
<tr>
<td>8b</td>
<td>3c</td>
<td>4-FPh</td>
<td>H</td>
<td>86</td>
</tr>
<tr>
<td>8c</td>
<td>3d</td>
<td>4-ClPh</td>
<td>H</td>
<td>71</td>
</tr>
<tr>
<td>8d</td>
<td>3e</td>
<td>4-BrPh</td>
<td>H</td>
<td>74</td>
</tr>
<tr>
<td>8e</td>
<td>3f</td>
<td>H</td>
<td>H</td>
<td>28</td>
</tr>
<tr>
<td>8f</td>
<td>3g</td>
<td>Me</td>
<td>H</td>
<td>54</td>
</tr>
<tr>
<td>8g</td>
<td>3h</td>
<td>H</td>
<td>Cl</td>
<td>53</td>
</tr>
<tr>
<td>9</td>
<td>3i</td>
<td>H</td>
<td>Br</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>3i</td>
<td>H</td>
<td>Br</td>
<td>32</td>
</tr>
</tbody>
</table>

The in situ-methodology was not suitable for the reaction with the structural different 1,3-biselectrophiles phenylpropinal (11), acetylacetone (12) and the phenyltrimethinium-perchlorate 13. Therefore we replaced ketene aminal 4K by a stable and pure primary/secondary ketene aminal 15, which could be synthesized by aminolysis of imidates 7Ia and 7Ib respectively with an appropriate amine. Liberation of imidates 7Ia.b from the hydrochlorides was easily performed by treatment of 7a-HCl and 7b-HCl with aqueous sodium bicarbonate solution. The 1H NMR-spectra in DMSO-d6 showed that imidates 7Ia.b exist in a tautomeric equilibrium with ketene-O,N-acetales 7Ea.b, this was also supported by NOE-data and C–H-correlations. The ratio 7Ia:7Ea in DMSO-d6 at 20 °C was nearly 1:2. In acetone-d6 or CDCl3, the ratio changed to the dominating imidate form 7Ia. Imidates 7Ib and 7Eb exist in DMSO-d6 at 20 °C in a 3:7 ratio. The isomers 7Za and 7Zb could not be detected in the NMR-spectra.

Treatment of imidate/ketene-O,N-acetal mixtures 7a and 7b respectively with (±)-1-phenylethylamine (14) in ethanol at room temperature afforded the primary/secondary ketene aminal 15, whose existence in the E-configuration was established by NOE-measurements (Scheme 4).
Scheme 5 shows that cyclocondensation of ketene aminal \( 15 \) with phenylpropinal \( 11 \), acetylacetone \( 12 \) and trimethinium salt \( 13 \) in boiling ethanol–acetic acid yielded \( N \)-(1-phenylethyl)-substituted phenyl 2-aminopyridine-3-sulfonates \( 16a-c \). A planned deprotection of the 1-phenylethyl group in \( 16a-c \) was managed by treatment with polyphosphoric acid at 60 °C \( 12-14 \) yielding pyridines \( 3a, j, k \) (Table 2).

The preparation of the aforementioned pyrido[2,3-\( e \)][1,2,4]thiadiazine-1,1-dioxides \( 2 \) started with the ammonolysis of \( 3g \), as an example, yielding 2-aminopyridine-sulfonamide \( 17 \). We found that usual methods e.g. heating \( 3g \) in ethanolic or aqueous ammonia or treatment with ammonium acetate in high boiling solvents failed. Only forced ammonolysis of \( 3g \) with liquid ammonia in a steel autoclave at 150 °C and 110 bar afforded the 2-aminopyridine-sulfonamide \( 17 \) in insufficient yield (8%).

\[
\text{Scheme 5} \quad \text{Table 2} \quad \text{Preparation of Pyridines 3a, j, k}
\]

<table>
<thead>
<tr>
<th>1,3-Bis-Electrophiles</th>
<th>Product</th>
<th>( R^1 )</th>
<th>( R^2 )</th>
<th>( R^3 )</th>
<th>Yield (%)</th>
<th>Mp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>( 11 )</td>
<td>3a</td>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>46</td>
<td>127–128</td>
</tr>
<tr>
<td>( 12 )</td>
<td>3j</td>
<td>Me</td>
<td>H</td>
<td>Me</td>
<td>83</td>
<td>134–135</td>
</tr>
<tr>
<td>( 13 )</td>
<td>3k</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>74</td>
<td>107–108</td>
</tr>
</tbody>
</table>

As expected the \( \sigma \)-aminosulfonamide \( 17 \) smoothly reacted with triethyl orthoformate \( 18a \) \((R = H)\) or triethyl orthoacetate \( 18b \) \((R = Me)\) giving the pyrido[2,3-\( e \)][1,2,4]thiadiazine-1,1-dioxides \( 2a \) and \( 2b \).

According to UV-data from Pirotte et al.\(^3\) \( 2a, b \) in methanol exist in a \( 4H \)-form as depicted in Scheme 6. They show \( \lambda_{\text{max}} \) below 290 nm \((2a: \lambda_{\text{max}} = 288 \text{ nm}, 2b: \lambda_{\text{max}} = 287 \text{ nm})\), which is typical of the \( 4H \)-form.

Melting points were determined on a Kofler hot stage apparatus (Reichert) and are uncorrected. All yields refer to pure isolated products. The IR spectra were obtained with a Perkin-Elmer Lambda 5 spectrometer in CHCl\(_3\) solution or as KBr pellets. \(^1\)H NMR and NOE-difference experiments were recorded in a Bruker AC 250 or Bruker AM 360 spectrometer in DMSO-\( d_6 \) with TMS as an internal standard. \(^13\)C NMR were recorded at 60 or 90 MHz on the same instruments in DMSO-\( d_6 \). For MS, the MAT TQS 70 apparatus (Finnigan) was used and the intensities are relative to the base peak (\( I = 100\% \)). The reactions under pressure were performed with a laboratory autoclave (Berghof) with PTFE vessel, variable heating source attached with mechanical stirrer. Column chromatography was performed on silica gel 60 (<0.063 mm, Macherey-Nagel). Elemental analyses were carried out by the Institut für Organische Chemie and Institut für Anorganische Chemie, Universität Erlangen-Nürnberg with CHN-Rapid (Heraeus) and Type 1106 and 1108 (Carlo Erba).

Phenyl carbamoylmethanesulfonate \( 6 \) was prepared based upon the method described by Hinman et al.\(^{11}\). The syntheses of \( \beta \)-amino-1-novinylketones were carried out according to a literature method.\(^{12}\) 3-Dimethylaminoacrolein \( 8f \), phenylpropinal \( 11 \) and acetylacetone \( 12 \) were purchased from Fluka and used without further purification.

Phenyl cyanomethanesulfonate \( 5 \) A suspension of \( 6 \) (4.30 g, 20 mmol) in freshly distilled phosphorus oxychloride (15 mL) was stirred for 2 h at 60–70 °C. The clear and cooled solution was evaporated in vacuo. The residue was dissolved in Et\(_2\)O (50 mL), washed with aq sat. NaHCO\(_3\) solution (\( 3 \times 20 \text{ mL} \)), H\(_2\)O (\( 3 \times 20 \text{ mL} \)), dried over Na\(_2\)SO\(_4\), filtered and the organic layer was evaporated in vacuo. The crude, oily and colorless product (2.82 g, 72%) was used without further purification.

\[
\text{IR (CHCl}_3\text{): } 3031, 2984, 2936, 2267, 1392, 1142 \text{ cm}^{-1}.
\]

\[
\text{\(^1\)H NMR (DMSO-}\text{d}_6\text{): } \delta = 5.58 (s, 2 \text{ H, CH}_2), 7.35–7.60 (m, 5 \text{ H, Ph}).
\]

\[
\text{\(^13\)C NMR (DMSO-}\text{d}_6\text{): } \delta = 39.7 (\text{CH}_2), 111.3 (\text{CN}), 121.9 (\text{C-2’, C-6’}), 128.1 (\text{C-4’}), 130.4 (\text{C-3’, C-5’}), 148.6 (\text{C-1’}).
\]

\[
\text{MS (EI, 70eV): } m/z (%): 197 (44) [M^+], 93 (63), 65 (100).
\]

Synthesis of Alkyl 2-(Phenoxy)sulfonyl)ethanimidoates Hydrochlorides (7a-HCl): General Procedure

Dry HCl was passed through a stirred solution of phenyl cyanomethanesulfonylhydrazine (5) (1.97 g, 10 mmol) and alcohol (12 mmol) in anhyd Et2O (30 mL) at 0°C over 2 h. After addition of Et2O (30 mL) the product crystallized completely on standing overnight at 4°C. Filtration of the mixture gave the salt.

Methyl 2-(Phenoxy)sulfonyl)ethanimidoate Hydrochloride (7a-HCl)
Colorless needles; yield: 2.40 g (90%); mp 95°C.

IR (KBr): 3391, 3050, 3014, 2975, 2904, 1662, 1387, 1142 cm⁻¹.

Phenyl 2-Aminopyridine-3-sulfonate (3a)

Phenyl 2-Amino-6-(4-chlorophenyl)pyridine-3-sulfonate (3d)
Anal. Calcd for C₁₇H₁₃ClN₂O₃S (360.82): C, 56.6; H, 3.63; N, 7.76.

Phenyl 2-Amino-6-(4-methoxyphenyl)pyridine-3-sulfonate (3b)

Phenyl 2-Amino-6-(4-bromophenyl)pyridine-3-sulfonate (3e)

Phenyl 2-Amino-6-(4-fluorophenyl)pyridine-3-sulfonate (3e)
IR (KBr): v = 3465, 3449, 3084, 1656, 1636, 1147 cm⁻¹.

Phenyl 2-Amino-6-(4-chlorophenyl)pyridine-3-sulfonate (3d)
Method A; colorless crystals; yield: 511 mg (71%); mp 134°C.

IR (KBr): 3453, 3306, 1639, 1572, 1364, 1147, 1070 cm⁻¹.

Phenyl 2-Amino-6-(4-bromophenyl)pyridine-3-sulfonate (3e)
Method A; colorless crystals; yield: 470 mg (67%); mp 148°C.

IR (KBr): 3461, 3312, 3081, 2965, 1605, 1571, 1358, 1145 cm⁻¹.

Phenyl 2-Amino-6-(4-methoxyphenyl)pyridine-3-sulfonate (3b)
Method A; colorless crystals; yield: 740 mg (67%); mp 134°C.
Phenyl 2-Amino-6-methylpyridine-3-sulfonate (3g)
Method A; colorless crystals; yield: 231 mg (54%); mp 124 °C.
IR (KBr): 3442, 3305, 3059, 1651, 1581, 1365, 1146 cm⁻¹.
Anal. Calcd for C₁₁H₉BrN₂O₃S (329.18): C, 40.1; H, 2.76; N, 8.51.
Phenyl 2-Amino-5-chloropyridine-3-sulfonate (3h)
Method A; colorless needles; yield: 300 mg (53%); mp 112–114 °C.
IR (KBr): 3460, 3307, 3058, 1585, 1366, 1147, 1072 cm⁻¹.
Phenyl 2-Amino-6-methylpyridine-3-sulfonate (3g)
Method A; colorless crystals; yield: 231 mg (54%); mp 124 °C.
IR (KBr): 3442, 3305, 3059, 1651, 1385, 1146 cm⁻¹.
1H NMR (DMSO-d₆): δ = 7.09–7.21 (m, 4 H, 2'-H, 3'-H, 4'-H, 6'-H), 7.30–7.55 (m, 3 H, 3'-H, 4'-H, 5'-H), 7.79 (d, J = 2.5 Hz, 1 H, 4'-H), 8.42 (d, J = 2.5 Hz, 1 H, 6'-H).
MS (El, 70 eV): m/z (%) = 329 (38/36) [M⁺], 237/235 (46/46), 173/171 (81/83), 94 (100).
Anal. Calcd for C₁₁H₉BrN₂O₃S (329/328): C, 40.1; H, 2.76; N, 8.51.

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1H NMR (DMSO-d₆): δ = 7.09–7.21 (m, 4 H, 2'-H, 3'-H, 4'-H, 6'-H), 7.30–7.55 (m, 3 H, 3'-H, 4'-H, 5'-H), 7.79 (d, J = 2.5 Hz, 1 H, 4'-H), 8.42 (d, J = 2.5 Hz, 1 H, 6'-H).
MS (El, 70 eV): m/z (%) = 329 (38/36) [M⁺], 237/235 (46/46), 173/171 (81/83), 94 (100).
Anal. Calcd for C₁₁H₉BrN₂O₃S (329/328): C, 40.1; H, 2.76; N, 8.51.
IR (CHCl₃): 3383, 3368, 3068, 3023, 2976, 2930, 1618, 1581, 1327, 1131 cm⁻¹.

1H NMR (DMSO-d₆): δ = 1.32 (d, J = 6.5 Hz, 3 H, CH₃CH₂), 3.74 (s, 1 H, CH₃), 4.51 (br s, 1 H, CH₂), 5.03 (d, J = 7 Hz, 1 H, CH), 6.37–7.10 (m, 3 H, NH, 2-H, 6'-H), 7.13–7.55 (m, 8 H, 3'-H, 4'-H, 5'-H, 2'-H, 3'-H, 4'-H, 5'-H, 6'-H). MS (EI, 70 eV): mz (%) = 318 (10) [M⁺], 161 (58), 105 (100).

Analysis. Calcd for C₁₆H₁₈N₂O₃S (318.40): C, 60.4; H, 5.70; N, 8.80.

2-(1-Phenylamino)-substituted Phenyl Pyridine-3-sulfonates 16; General Procedure

Ketoneamine 15 (0.64 g, 2 mmol) and 1,3-biselectrophiles 11, 12 or 13 (2 mmol) were refluxed in EtOH–HOAc (20 mL, 4:1) for 5 h. After evaporation under reduced pressure the products 16 were purified by column chromatography on silica gel with cyclohexane–EtOAc (4:1) and then crystallized from EtOH-acetone.

(±)-Phenyl 6-Phenyl-2-(1-phenylamino)pyridine-3-sulfonate (16a)

Colorless crystals; yield: 300 mg (35%); mp 91.5–92 °C.

IR (KBr): 3450, 3375, 1300, 1151 cm⁻¹.

UV (MeOH): λ_max (log ε) = 207 nm (4.646), 264 (4.172), 298 (sh, 3.646).

Analysis. Calcd for C₁₆H₁₈N₂O₃S (318.40): C, 60.4; H, 5.70; N, 8.80.

2-Amino-6-methylpyridine-3-sulfonamide (17)

Phenyl 2-amino-6-methylpyridine-3-sulfonate (3g) (1.32 g, 5 mmol) in liquid NH₃ (40 mL) was placed at –50 °C in an autoclave and heated for 48 h at 150 °C. The temperature was allowed to rise to r.t., the residue was dissolved with EtOH (30 mL) in the course of which the educt 3g (ca. 1.06 g, 80%) was recovered by crystallization at 4 °C. The filtrate was concentrated under reduced pressure and the residue purified by column chromatography on silica gel in CHCl₃–MeOH (9:1) as eluent to yield a beige amorphous product (75 mg, 8%); mp >310 °C.

IR (KBr): 3450, 3375, 1300, 1131 cm⁻¹.

1H NMR (DMSO-d₆): δ = 2.30 (s, 3 H, CH₃), 6.42 (br s, 2 H, NH₂), 6.53 (d, J = 8 Hz, 1 H, 5-H), 7.44 (br s, 2 H, NH₂), 7.74 (d, J = 8 Hz, 1 H, 4-H).

MS (EI, 70 eV): mz (%) = 187 (100) [M⁺], 123 (39), 107 (100).


6-Methyl-4H-pyrido[2,3-c][1,2,4]thiadiazine-1,1-dioxide (2a)

2-Amino-6-methylpyridine-3-sulfonamide (17) (47 mg, 0.25 mmol) was stirred in triethyl orthoformate (4 mL) at 45 °C for 1 h. After evaporating the solvent in vacuo at 25 °C the remaining oil was purified by column chromatography on silica gel in CHCl₃–MeOH (9:1) as eluent, beige powder; yield: 43 mg (88%); mp 307 °C.

IR (KBr): 3187, 3117, 2976, 1615, 1532, 1372, 1140 cm⁻¹.

1H NMR (DMSO-d₆): δ = 2.55 (s, 3 H, CH₃), 7.40 (d, J = 8 Hz, 1 H, 7-H), 8.01 (s, 1 H, 3-H), 8.21 (s, J = 8 Hz, 1 H, 8-H), 12.65 (br s, 1 H, NH). MS (EI, 70 eV): mz (%) = 197 (51) [M⁺], 133 (100), 109 (99).

UV (MeOH): λ_max (log ε) = 204 nm (4.188), 270 (sh, 3.651), 288 (3.664).

Analysis. Calcd for C₁₆H₁₄N₂O₃S (211.25): C, 58.7; H, 3.85; N, 19.7. Found: C, 58.5; H, 3.8; N, 19.7.

3,6-Dimethyl-4H-pyrido[2,3-c][1,2,4]thiadiazine-1,1-dioxide (2b)

Prepared according to 2a from 17 (47 mg, 0.25 mmol) and triethyl orthoformate (4 mL); beige powder; yield: 20 mg (38%); mp >310 °C.

IR (KBr): 3288, 2935, 1661, 1541, 1375, 1138 cm⁻¹.

1H NMR (CDCl₃): δ = 2.44 (s, 3 H, CH₃), 2.55 (s, 3 H, CH₃), 7.22 (d, J = 8 Hz, 1 H, 7-H), 8.14 (d, J = 8 Hz, 1 H, 8-H), 11.8 (br s, 1 H, NH).

MS (EL, 70 eV): mz (%) = 211 (77) [M⁺], 170 (93), 105 (100).

UV (MeOH): λ_max (log ε) = 207 nm (4.646), 264 (4.172), 298 (sh, 4.397).


References


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