Synthesis of Substituted Phenyl 2-Aminopyridine-3-sulfonates

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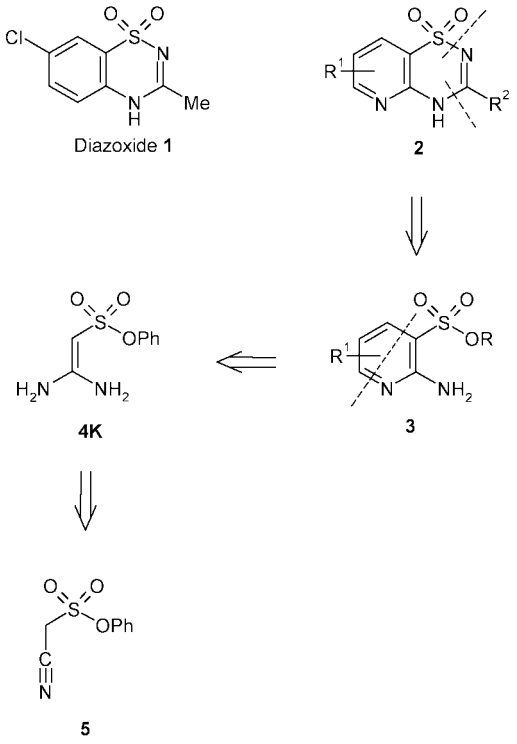
Abstract: A series of phenyl 2-aminopyridine-3-sulfonates **3** has been synthesized starting from phenyl cyanomethanesulfonate (**5**). Pinner reaction with **5** gave phenoxysulfonylketene aminal **4K** which was cyclocondensed with a series of C_3-biselectrophiles to yield the title compounds, which 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** (R^1 = Ar, Alk, Hal; R^2 = H, Me). A short retrosynthetic view will explain our approach (Scheme 1). Title compounds **3** were considered to be prepared by an C_3–C_2N-pyridine synthesis[6–9] via diprimary phenoxysulfonylketene aminal **4K**, which could be generated from the key starting material phenyl cyanomethanesulfonate (**5**).

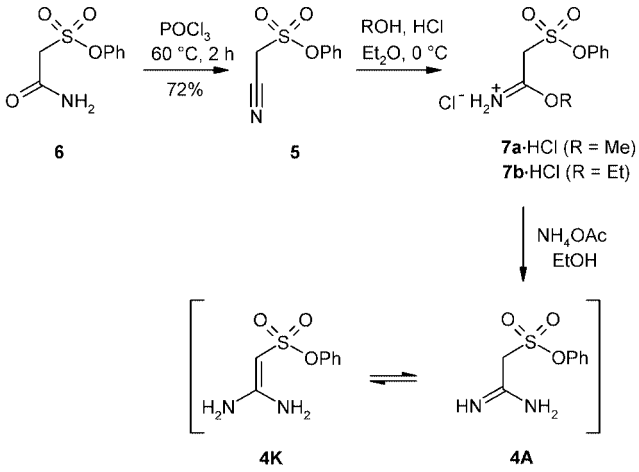


Scheme 1

Krutak et al.[10] reported the synthesis of **5,** without giving experimental details. Phenyl cyanomethanesulfonate (**5**) can easily be prepared by dehydration of amide **6**[11] 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 -aldehyde **8f** respectively and gave rise to 5- and 6-substituted 2-aminopyridines **3a**–**g** (Scheme 3).



Scheme 2

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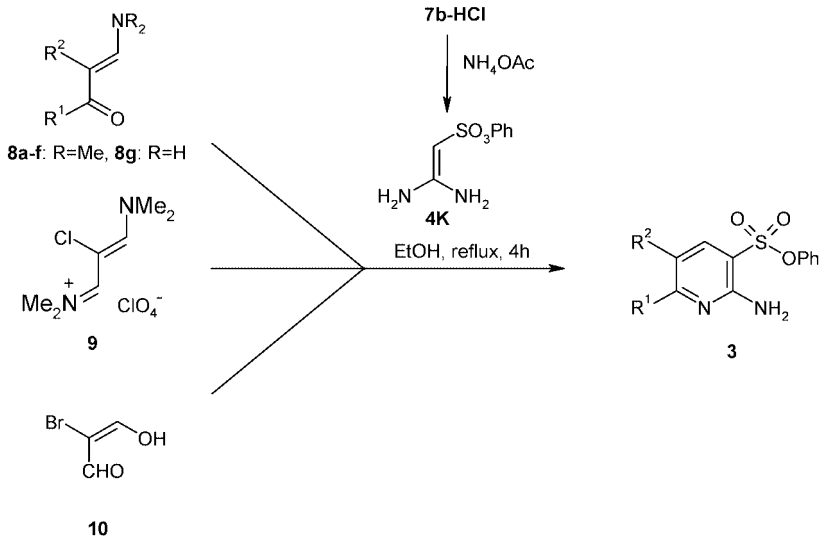


Scheme 3

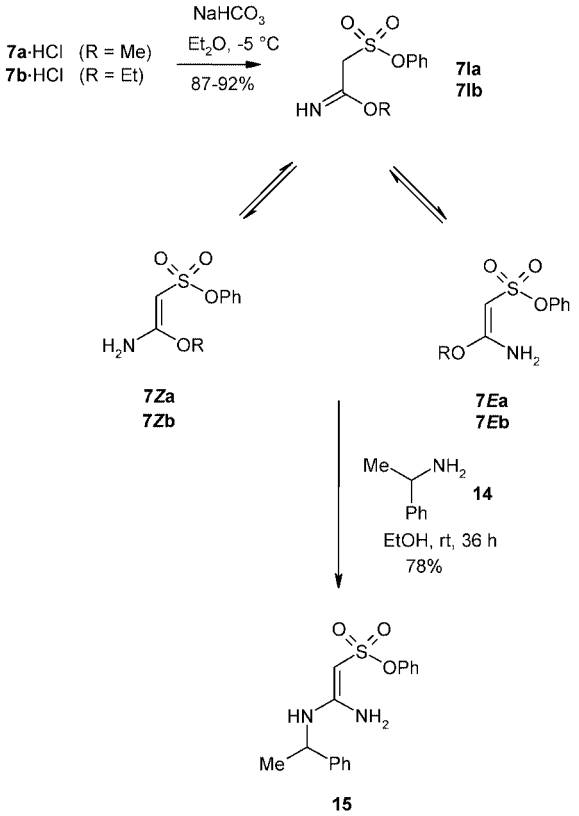
The trimethinium salt **9** and bromomalonaldehyde (**10**) were reacted with **4K** yielding the pyridines **3h** and **3i** (Table 1).

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

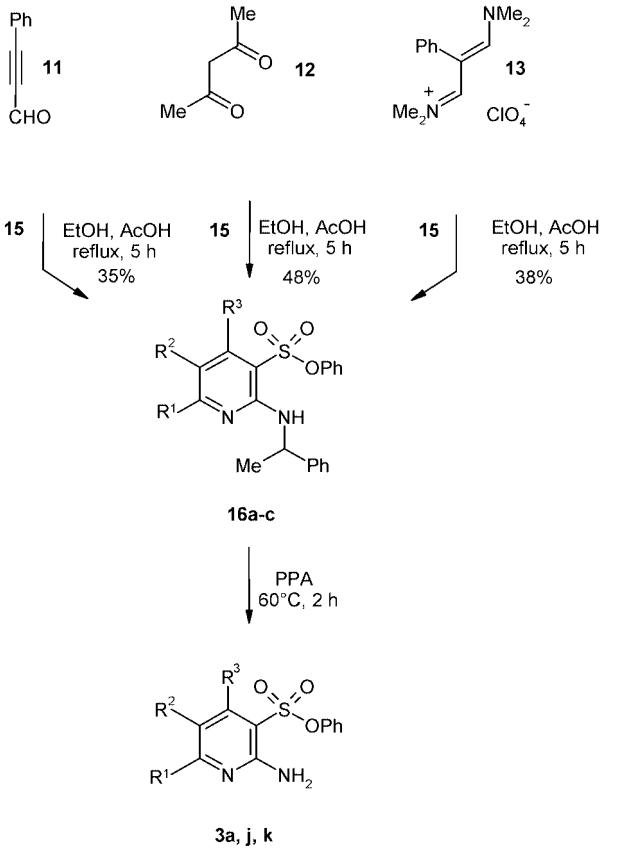
1,3-Bis-Nucleophiles	Product	R^1	R^2	Yield (%)	Mp (°C)
8a	**3a**	Ph	H	76	127–129
8b	**3b**	4-MeOPh	H	67	148
8c	**3c**	4-FPh	H	86	112
8d	**3d**	4-ClPh	H	71	134
8e	**3e**	4-BrPh	H	74	136–137
8f	**3f**	H	H	28	103–104
8g	**3g**	Me	H	54	124
9	**3h**	H	Cl	53	112–114
10	**3i**	H	Br	32	130–132

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 ^{1}H NMR-spectrum in DMSO-d_6 showed that imidates **7 Ia**,**b** exist in a tautomeric equilibrium with ketene-*O*,*N*-acetales **7*E*a**,**b**, this was also supported by NOE-data and C–H-correlations. The ratio **7Ia**:**7*E*a** in DMSO-d_6 at 20 °C was nearly 1:2. In acetone-d_6 or $CDCl_3$ the ratio changed to the dominating imidate form **7Ia**. Imidates **7Ib** and **7*E*b** exist in DMSO-d_6 at 20 °C in a 3:7 ratio. The isomers **7*Z*a** and **7*Z*b** 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 4



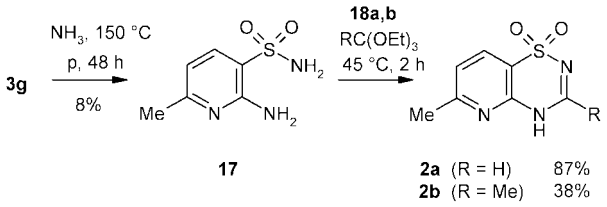
Scheme 5

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-phenylethylgroup 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-amino-6-methylpyridine-3-sulfonamide (**17**) in insufficient yield (8%).

Table 2 Preparation of Pyridines **3a**,**j**,**k**

1,3-Bis-Electrophiles	Product	R^1	R^2	R^3	Yield (%)	Mp (°C)
11	**3a**	Ph	H	H	46	127–128
12	**3j**	Me	H	Me	83	134–135
13	**3k**	H	Ph	H	74	107–108



Scheme 6

As expected the *o*-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 4*H*-form as depicted in Scheme 6. They show a λ_{max} below 290 nm (**2a**: 288 nm, **2b**: 287 nm), which is typical of the 4*H*-form.

Melting points were determinated 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 on 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 β-aminovinylketones 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 phosphorous oxychloride (15mL) was stirred for 2 h at 60–70 °C. The clear and cooled solution was evaporated in vacuo. The residue was dissolved in Et_2O (50 mL), washed with aq sat. $NaHCO_3$ solution (3 × 20 mL), H_2O (3 × 20 mL), dried over Na_2SO_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.

IR ($CHCl_3$): 3031, 2984, 2936, 2267, 1392, 1142 cm^{-1}.

^{1}H NMR (DMSO-d_6): δ = 5.58 (s, 2 H, CH_2), 7.35–7.60 (m, 5 H, Ph).

^{13}C NMR (DMSO-d_6): δ = 39.7 (CH_2), 111.3 (CN), 121.9 (C-2′, C-6′), 128.1 (C-4′), 130.4 (C-3′, C-5′), 148.6 (C-1′).

MS (EI, 70eV): *m*/*z* (%) = 197 (44) [M$^+$], 93 (63), 65 (100).

Anal. Calcd for $C_8H_7NO_3S$ (197.21): C, 48.70, H, 3.58, N, 7.10. Found: C, 48.40, H, 3.51, N, 7.39.

Synthesis of Alkyl 2-(Phenoxysulfonyl)ethanimidoates Hydrochlorides (7·HCl); General Procedure

Dry HCl was passed through a stirred solution of phenyl cyanomethanesulfonate (**5**) (1.97 g, 10 mmol) and alcohol (12 mmol) in anhyd Et_2O (30 mL) at 0 °C over 2 h. After addition of Et_2O (30 mL) the product crystallized completely on standing overnight at 4 °C. Filtration of the mixture gave the salt.

Methyl 2-(Phenoxysulfonyl)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}.

^1H NMR (DMSO-d_6): = 3.76 (s, 3 H, OCH_3), 4.88 (s, 2 H, CH_2), 7.33–7.55 (m, 5 H, Ph), 7.80 (s, 2 H, NH_2).

MS (EI, 70 eV): *m*/*z* (%) = 230 (27) [M^+ – Cl], 94 (100).

Anal. Calcd for $C_9H_{12}ClNO_4S$ (265.72): C, 40.7; H 4.55; N, 5.27. Found: C, 40.7; H, 4.24, N, 5.67.

Ethyl 2-(Phenoxysulfonyl)ethanimidoate Hydrochloride (7b·HCl)

Colorless needles; yield: 2.69 g (96%); mp 105–106 °C.

IR (KBr): 3369, 2995, 2946, 1381, 1143 $cm^{-1.}$

^1H NMR (DMSO-d_6): δ = 1.23 (t, *J* = 7 Hz, 3 H, OCH_2CH_3), 4.22 (q, *J* = 7 Hz, 2 H, OCH_2CH_3), 4.85 (s, 2 H, CH_2), 7.10 (s, 2 H, NH_2), 7.36–7.55 (m, 5 H, Ph).

MS (EI, 70 eV): *m*/*z* (%) = 244 (24) [M^+ – Cl], 94 (100).

Anal. Calcd for $C_{10}H_{14}ClNO_4S$ (279.74): C, 42.9; H, 5.04; N, 5.01. Found: C, 43.0; H, 5.26; N, 4.65.

Synthesis of Phenyl 2-Aminopyridine-3-sulfonates 3; General Procedure

Method A

7b·HCl (560 mg, 2 mmol), ammonium acetate (2 g) and **8a**–**g** (2 mmol)**, 9** (2 mmol), or **10** (2 mmol) were refluxed in EtOH (20 mL) for 4 h. Cooling at 4 ° C overnight yielded the product as a crystalline solid.

Method B

(±)-Phenyl 2-[1-(phenylethyl)amino]pyridine-3-sulfonates **16a**–**c** (0.5 mmol) were heated with polyphosphoric acid (PPA) (4 g) for 2 h at 60 °C. After cooling to r.t. the mixture was hydrolyzed with ice-water (15 mL) and neutralized with concd NH_3. The thus formed precipitate was filtered and crystallized from EtOH.

Phenyl 2-Amino-6-phenylpyridine-3-sulfonate (3a)

Colorless needles; yield: 495 mg (76%, method A), 75 mg (46%, method B); mp 127–129 °C.

IR (KBr): 3400, 3066, 1608, 1573, 1560, 1357, 1144 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 6.97 (br s, 2 H, NH_2), 7.10–7.18 (m, 2 H, 2″-H, 6″-H), 7.26 (d, *J* = 8 Hz, 1 H, 5-H), 7.28–7.46 (m, 3 H, 3″-H, 4″-H, 5″-H), 7.47–7.55 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.78 (d, *J* = 8 Hz, 1 H, 4-H), 8.08–8.14 (m, 2 H, 2′-H, 6′-H).

^{13}C NMR (DMSO-d_6): δ = 108.7, 109.6 (C-3, C-5), 122.5 (C-2″, C-6″), 127.9, 129.6, 131.5 (C-2′, C-3′, C-4′, C-5′, C-6′), 128.4 (C-4″), 130.8 (C-3″, C-5″), 137.3 (C-1′), 141.7 (C-4), 149.4 (C-1″), 155.9, 160.0 (C-2, C-6).

MS (EI, 70 eV): *m*/*z* (%) = 326 (32) [M^+], 233 (52), 185 (19), 169 (100).

Anal. Calcd for $C_{17}H_{14}N_2O_3S$ (326.38): C, 62.6; H, 4.32; N, 8.58. Found: C, 62.6; H, 4.66; N, 8.53.

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

Method A; colorless crystals; yield: 470 mg (67%); mp 148 °C.

IR (KBr): 3461, 3312, 3081, 2965, 1605, 1571, 1358, 1145 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 3.83 (s, 3 H, OCH_3), 6.89 (br s, 2 H, NH_2), 7.01–7.09 (m, 2 H, 3′-H, 5′-H), 7.10–7.16 (m, 2 H, 2″-H, 6″-H), 7.19 (d, *J* = 8 Hz, 1 H, 5-H), 7.26–7.46 (m, 3 H, 3″-H, 4″-H, 5″-H), 7.71 (d, *J* = 8 Hz, 1 H, 4-H), 8.02–8.11 (m, 2 H, 2′-H, 6′-H).

MS (EI, 70 eV): *m*/*z* (%) = 356 (38) [M^+], 263 (63), 215 (79), 199 (100).

Anal. Calcd for $C_{18}H_{16}N_2O_4S$ (356.40): C, 60.7; H, 4.53; N, 7.86. Found: C, 60.8; H, 4.16; N, 7.79.

Phenyl 2-Amino-6-(4-fluorophenyl)pyridine-3-sulfonate (3c)

Method A; colorless needles; yield: 591 mg (86%); mp 112 °C.

IR (KBr): 3460, 3307, 1639, 1569, 1369, 1145, 1163 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 6.97 (br s, 2 H, NH_2), 7.09–7.17 (m, 2 H, 2″-H, 6″-H), 7.24 (d, *J* = 8 Hz, 1 H, 5-H), 7.28–7.46 (m, 5 H, 3′-H, 5′-H, 3″-H, 4″-H, 5″-H), 7.77 (d, *J* = 8 Hz, 1 H, 4-H), 8.10–8.20 (m, 2 H, 2′-H, 6′-H).

MS (EI, 70 eV): *m*/*z* (%) = 344 (45) [M^+], 251 (81), 203 (34), 187 (100).

Anal. Calcd for $C_{17}H_{13}FN_2O_3S$ (344.37): C, 59.3; H, 3.81; N, 8.13. Found: C, 58.9, H, 3.74; N, 8.42.

Phenyl 2-Amino-6-(4-chlorophenyl)pyridine-3-sulfonate (3d)

Method A; colorless crystals; yield: 511 mg (71%); mp 134 °C.

IR (KBr): 3452, 3306, 1639, 1572, 1365, 1148, 1091 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 6.99 (br s, 2 H, NH_2), 7.09–7.17 (m, 2 H, 2″-H, 6″-H), 7.26 (d, *J* = 8 Hz, 1 H, 5-H), 7.28–7.46 (m, 3 H, 3″-H, 4″-H, 5″-H), 7.54–7.62 (m, 2 H, 3′-H, 5′-H), 7.79 (d, *J* = 8 Hz, 1 H, 4-H), 8.07–8.15 (m, 2 H, 2′-H, 6′-H).

MS (EI, 70 eV): *m*/*z* (%) = 362/360 (34/95) [M^+], 269/267 (35/97), 221/219 (10/30), 205/203 (30/100), 168 (100).

Anal. Calcd for $C_{17}H_{13}ClN_2O_3S$ (360.82): C, 56.6; H, 3.63; N, 7.76. Found: C, 56.9; H, 3.52; N, 7.78.

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

Method A; colorless needles; yield: 600 mg (74%); mp 136–137 °C.

IR (KBr): 3453, 3306, 1639, 1572, 1364, 1147, 1070 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.00 (br s, 2 H, NH_2), 7.09–7.18 (m, 2 H, 2″-H, 6″-H), 7.26 (d, *J* = 8 Hz, 1 H, 5-H), 7.28–7.46 (m, 3 H, 3″-H, 4″-H, 5″-H), 7.68–7.75 (m, 2 H, 3′-H, 5′-H), 7.79 (d, *J* = 8 Hz, 1 H, 4-H), 8.00–8.08 (m, 2 H, 2′-H, 6′-H).

MS (EI, 70 eV): *m*/*z* (%) = 406/404 (22/21) [M^+], 313/311 (39/38), 249/247 (15/15), 168 (100).

Anal. Calcd for $C_{17}H_{13}BrN_2O_3S$ (405.28): C, 50.9; H, 3.27, N, 6.98. Found: C, 51.0; H, 3.29; N, 7.04.

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

Method A; colorless needles; yield: 140 mg (28%); mp 103–104 °C.

IR (KBr): v = 3465, 3449, 3084, 1656, 1636, 1364, 1174 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 6.65 (dd, J_1 = 8 Hz, J_2 = 4.5 Hz, 1 H, 5-H), 6.89 (br s, 2 H, NH_2), 7.05–7.13 (m, 2 H, 2′-H, 6′-H), 7.27–7.45 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.70 (dd, J_1 = 8 Hz, J_3 = 2 Hz, 1 H, 4-H), 8.31 (dd, J_2 = 4.5 Hz, J_3 = 2 Hz, 1 H, 6-H).

MS (EI, 70 eV): *m*/*z* (%) = 250 (15) [M^+], 157 (33), 93 (100).

Anal. Calcd for $C_{11}H_{10}N_2O_3S$ (250.28): C, 52.8; H, 4.02; N, 11.19. Found: C, 53.0; H, 4.12; N, 11.19.

Phenyl 2-Amino-6-methylpyridine-3-sulfonate (3g)
Method A; colorless crystals; yield: 231 mg (54%); mp 124 °C.

IR (KBr): 3441, 3309, 3064, 3047, 2991, 2983, 1728, 1332, 1146 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.33 (s, 3 H, CH_3), 6.52 (d, *J* = 8 Hz, 1 H, 5-H), 6.80 (br s, 2 H, NH_2), 7.04–7.12 (m, 2 H, 2′-H, 6′-H), 7.25–7.45 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.57 (d, *J* = 8 Hz, 1 H, 4-H).

MS (EI, 70 eV): *m*/*z* (%) = 264 (41) [M^+], 171 (72), 107 (100).

Anal. Calcd for $C_{12}H_{12}N_2O_3S$ (264.31): C, 54.5; H, 4.58; N, 10.60. Found: C, 54.7; H, 4.81; N, 10.48.

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, 1640, 1585, 1366, 1147, 1072 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.05–7.25 (m, 4 H, 2′-H, 6′-H, NH_2), 7.30–7.55 (m, 3 H, 3′-H, 4′-H, 5′-H), 7.72 (d, *J* = 2.5 Hz, 1 H, 4-H), 8.37 (d, *J* = 2.5 Hz, 1 H, 6-H).

MS (EI, 70 eV): *m*/*z* (%) = 284 (1) [M^+], 244 (11), 94 (100).

Anal. Calcd for $C_{11}H_9ClN_2O_3S$ (284.72): C, 46.4; H, 3.19; N, 9.84. Found: C, 46.2; H, 3.45; N, 10.10.

Phenyl 2-Amino-5-bromopyridine-3-sulfonate (3i)
Method A; colorless crystals; yield: 210 mg (32%); mp 130–132 °C.

IR (KBr): 3442, 3305, 3059, 1651, 1581, 1365, 1146, 1071 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.09–7.21 (m, 4 H, NH_2, 2′-H, 6′-H), 7.30–7.50 (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 (EI, 70 eV): *m*/*z* (%) = 330/328 (38/36) [M^+], 237/235 (46/46), 173/171 (81/83), 94 (100).

Anal. Calcd for $C_{11}H_9BrN_2O_3S$ (329.18): C, 40.1; H, 2.76; N, 8.51. Found: C, 40.5; H, 2.65; N, 8.53.

Phenyl 2-Amino-4,6-dimethylpyridine-3-sulfonate (3j)
Method B from **16b**; colorless needles; yield: 100 mg (83%); mp 107–108 °C.

IR (KBr): 3467, 3394, 3165, 1579, 1555, 1358, 1146 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.34 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3), 5,90 (br s, 2 H, NH_2), 6.40 (s, 1 H, H-5), 7.04–7.09 (m, 2 H, 2′-H, 6′-H) 7.22–7.35 (m, 3 H, 3′-H, 4′-H, 5′-H).

MS (EI, 70 eV): *m*/*z* (%) = 278 (36) [M^+], 185 (100), 121 (91), 80 (59).

Anal. Calcd for $C_{13}H_{14}N_2O_3S$ (278.33): C, 56.1; H, 5.07; N 10.06. Found: C 56.3, H 5.10, N 10.13.

Phenyl 2-Amino-5-phenylpyridine-3-sulfonate (3k)
Method B from **16c**; colorless crystals; yield: 160 mg (74%); mp 134–135 °C.

IR (KBr): 3476, 3060, 3029, 1637, 1604, 1507, 1483, 1358, 1143 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 7.07 (br s, 2 H, NH_2), 7.12–7.20 (m, 2 H, 2″-H, 6″-H), 7.27–7.55 (m, 8 H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H, 3″-H, 4″-H, 5″-H), 7.86 (d, *J* = 2.5 Hz, 1 H, 4-H), 8.68 (d, *J* = 2.5 Hz, 1 H, 6-H).

MS (EI, 70 eV): *m*/*z* (%) = 326 (29) [M^+], 233 (12), 185 (16), 169 (100).

Anal. Calcd for $C_{17}H_{14}N_2O_3S$ (326.37): C, 62.6, H, 4.32; N, 8.58. Found: C, 62.2; H, 4.26; N, 8.78.

Imidates 7 from Imidate Hydrochlorides 7·HCl; General Procedure
To a mixture of H_2O (40 mL), Et_2O (40 mL) and $NaHCO_3$ (2.5 g) cooled by an ice bath **7a**·HCl and **7b**·HCl respectively (15 mmol) were added over 30 min in small portions. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 30 mL). The organic phase was washed with H_2O (20 mL) and dried ($MgSO_4$) and the solvent evaporated in vacuo at 20 °C to give an oil which was used without further purification.

(*E*)-Phenyl 2-Amino-2-methoxyethensulfonate (7-*E*a) and Methyl-2-(Phenoxysulfonyl)-ethanimidoate (7Ia)
Colorless oil; yield: 3.0 g (87%).

7-*E*a
^1H NMR (DMSO-d_6): δ = 3.63 (s, 3 H, OCH_3), 4.40 (s, 1 H, 1-H), 6.81 (br s, 2 H, NH_2), 7.20–7.55 (m, 5 H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H).

^{13}C NMR (DMSO-d_6): δ = 56.0 (OCH_3), 63.5 (C-1), 122.5 (C-2′, C-6′), 126.4 (C-4′), 129.5 (C-3′, C-5′), 150.0 (C-1′), 167.1 (C-2).

7-Ia
^1H NMR (DMSO-d_6): δ = 3.68 (s, 3 H, OCH_3), 4.65 (s, 2 H, CH_2), 7.20–7.55 (m, 5 H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H), 8.78 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 53.3 (OCH_3), 54.7 (CH_2), 122.1 (C-2′, C-6′), 127.5 (C-4′), 130.1 (C-3′, C-5′), 148.9 (C-1′), 159.4 [*C*(OEt)=NH].

MS (EI, 70 eV): *m*/*z* (%) = 229 (2) [M^+], 136 (18), 94(100).

Anal. Calcd for $C_9H_{11}NO_4S$ (229.26): C, 47.2; H, 4.83; N, 6.11. Found: C, 47.0; H, 4.74; N, 5.95.

(*E*)-Phenyl 2-Amino-2-ethoxyethensulfonate (7-*E*b) and Ethyl 2-(Phenoxysulfonyl) ethanimidoate (7-Ib)
Colorless oil; yield: 3.36 g (80%).

7-*E*b
^1H NMR (DMSO-d_6): δ = 1.20 (t, *J* = 7 Hz, 3 H, OCH_2CH_3), 3.93 (q, J = 7 Hz, 2H, OCH_2CH_3), 4.37 (s, 1 H, 1-H), 6.80 (br s, 2 H, NH_2), 7.20–7.55 (m, 5 H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H).

^{13}C NMR (DMSO-d_6): δ = 14.0 (OCH_2CH_3), 63.7 (C-1), 64.5 (OCH_2CH_3), 122.4 (C-2′, C-6′), 126.3 (C-4′), 129.5 (C-3′, C-5′), 150.0 (C-1′), 166.2 (C-2).

7-Ib
^1H NMR (DMSO-d_6): δ = 1.22 (t, *J* = 7 Hz, 3 H, OCH_2CH_3), 4.13 (q, *J* = 7 Hz, 2 H, OCH_2CH_3), 4.62 (s, 2 H, CH_2), 7.20–7.55 (m, 5 H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H), 8.70 (br s, 1 H, NH).

^{13}C NMR (DMSO-d_6): δ = 13.8 (OCH_2CH_3), 54.8 (CH_2), 61.5 (OCH_2CH_3), 122.1 (C-2′, C-6′), 127.4 (C-4′), 130.1 (C-3′, C-5′), 148.9 (C-1′), 158.8 [*C*(OEt)=NH].

MS (EI, 70 eV): *m*/*z* (%) = 243 (1) [M^+], 198 (1), 94 (100).

Anal. Calcd for $C_{10}H_{13}NO_4S$ (243.28): C, 49.4; H, 5.39; N, 5.76. Found: C, 49.7; H, 5.72; N, 5.54.

(±)-(*E*)-Phenyl 2-Amino-2-[1-(phenylethyl)amino]ethensulfonate (15)
Compound **7-Ib** (3 mmol) was dissolved in EtOH (20 mL) and the mixture was stirred after addition of (±)-1-phenylethylamine (**14**) (360 mg, 3 mmol) for 72 h at r.t. The yellow solution was evaporated under reduced pressure. To the oily residue, of EtOH–Et_2O (30 mL, 2:1) was added to obtain a beige amorphous product (750 mg, 78%); mp 78–79 °C.

IR ($CHCl_3$): 3383, 3368, 3068, 3023, 2976, 2930, 1618, 1581, 1327, 1131 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.32 (d, J = 6.5 Hz, 3 H, CHCH_3), 3.74 (s, 1 H, 1-H), 4.51 (br s, 1 H, CHCH$_3$), 6.03 (br s, 2 H, NH_2), 6.87–7.10 (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): m/z (%) = 318 (10) [M^+], 161 (58), 105 (100).

Anal. Calcd for $C_{16}H_{18}N_2O_3S$ (318.40): C, 60.4; H, 5.70; N, 8.80. Found: C, 60.5; H, 5.31; N, 8.86.

2-[(1-Phenylethyl)amino]-substituted Phenyl Pyridine-3-sulfonates 16; General Procedure

Keteneaminal **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-phenylethyl)amino]pyridine-3-sulfonate (16a)

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

IR (KBr): 3400, 3065, 3023, 2971, 2924, 1572, 1590, 1357, 1145 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.53 (d, J_1 = 7 Hz, 3 H, CHCH_3), 5.43 (qd, J_1 = J_2 = 7 Hz, 1H, CHCH$_3$), 6.72 (d, J_2 = 7 Hz, 1 H, NH), 7.02–7.11 (m, 2 H, 2′′′-H, 6′′′-H), 7.18–7.52 (m, 11 H, 3′-H, 4′-H, 5′-H, 2′′-H, 3′′-H, 4′′-H, 5′′-H, 6′′-H, 3′′′-H, 4′′′-H, 5′′′-H), 7.30 (d, J_3 = 8.5 Hz, 1 H, 5-H), 7.87 (d, J_3 = 8.5 Hz, 1 H, 4-H), 7.93–8.05 (m, 2 H, 2′-H, 6′-H).

MS (EI, 70 eV): m/z (%) = 430 (24) [M^+], 415 (31), 105 (100).

Anal. Calcd for $C_{25}H_{22}N_2O_3S$ (430.53): C, 69.7; H, 5.15; N, 6.51. Found: C, 69.9; H, 5.18, N, 6.57.

(±)-Phenyl 4,6-Dimethyl-2-[(1-phenylethyl)amino]pyridine-3-sulfonate (16b)

Colorless crystals; yield: 370 mg (48%); mp 115 °C.

IR (KBr): 3414, 3099, 3027, 2966, 2924, 1587, 1558, 1355, 1166 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.31 (d, J_1 = 7 Hz, 3 H, CHCH_3), 2.23 (s, 3 H, CH$_3$), 2.44 (s, 3 H, CH$_3$), 5.20 (qd, J_1 = J_2 = 7 Hz, 1 H, CHCH$_3$), 6.52 (s, 1 H, H-5), 7.02–7.48 (m, 11 H, NH, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H, 2′′-H, 3′′-H, 4′′-H, 5′′-H, 6′′H,).

MS (EI, 70 eV): m/z (%) = 382 (38) [M^+], 367 (51), 105 (100).

Anal. Calcd for $C_{21}H_{22}N_2O_3S$ (382.48): C, 65.9; H, 5.80; N, 7.32. Found: C, 66.1; H, 5.67; N, 7.43.

(±) Phenyl 5-Phenyl-2-[(1-phenylethyl)amino]pyridine-3-sulfonate (16c)

Colorless crystals; yield: 330 mg (38%); mp 89.5–90.5 °C.

IR (KBr): 3422, 3060, 3027, 2924, 1604, 1581, 1565, 1370, 1148 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 1.50 (d, J_1 = 7 Hz, 3 H, CHCH_3), 5.40 (qd, J_1 = J_2 = 7 Hz, 1H, CHCH$_3$), 6.75 (d, J_2 = 7 Hz, 1 H, NH), 7.05–7.13 (m, 2 H, 2′′′-H, 6′′′-H), 7.20–7.47 (m, 11 H, 3′-H, 4′-H, 5′-H, 2′′-H, 3′′-H, 4′′-H, 5′′-H, 6′′, 3′′′-H, 4′′′-H, 5′′′-H), 7.49–7.57 (m, 2 H, 2′-H, 6′-H), 7.96 (d, J_3 = 2.5 Hz, 1 H, 4-H), 8.72 (d, J_3 = 2.5 Hz, 1 H, 6-H).

MS (EI, 70 eV): m/z (%) = 430 (30) [M^+], 415 (51), 105 (100).

Anal. Calcd for $C_{25}H_{22}N_2O_3S$ (430.53): C, 69.70; H, 5.15; N, 6.51. Found: C, 69.80; H, 4.84; N, 6.91.

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

Phenyl 2-amino-6-methylpyridine-3-sulfonate (**3g**) (1.32 g, 5 mmol) in liquid NH_3 (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 $CHCl_3$–MeOH (9:1) as eluent to yield a beige amorphous product (75 mg, 8%); mp >310 °C.

IR (KBr): 3450, 3375, 1300, 1151 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.30 (s, 3 H, CH_3), 6.42 (br s, 2 H, NH_2), 6.53 (d, J = 8 Hz, 1 H, 5-H) 7.44 (br s, 2 H, NH_2), 7.74 (d, J = 8 Hz, 1 H, 4-H).

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

Anal. Calcd for $C_6H_9N_3O_2S$ (187.22): C, 38.5; H, 4.85; N, 22.44. Found: C, 38.3; H, 4.59; N, 22.51.

6-Methyl-4*H*-pyrido[2,3-*e*][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 $CHCl_3$–MeOH (9:1) as eluent, beige powder; yield: 43 mg (88%); mp 307 °C.

IR (KBr): 3187, 3117, 2964, 1615, 1532, 1372, 1140 cm^{-1}.

^1H NMR (DMSO-d_6): δ = 2.55 (s, 3 H, CH_3), 7.40 (d, J = 8 Hz, 1 H, 7-H), 8.01 (s, 1 H, 3-H), 8.21 (d, J = 8 Hz, 1 H, 8-H), 12.65 (br s, 1 H, NH).

MS (EI, 70 eV): m/z (%) = 197 (51) [M^+], 133 (100), 105 (99).

UV (MeOH): λ_{max} (log ε) = 204 nm (4.188), 270 (sh, 3.651), 288 (3.864).

Anal. Calcd for $C_7H_7N_3O_2S$ (197.22): C, 42.6; H, 3.58; N, 21.31. Found: C, 42.30; H, 3.35; N, 21.0.

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

Prepared according to **2a** from **17** (47 mg, 0,25 mmol) and triethyl orthoacetate (4mL); beige powder; yield: 20 mg (38%); mp > 310 °C.

IR (KBr): 3288, 2935, 1661, 1541,1375, 1138 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.44 (s, 3 H, CH_3), 2.55 (s, 3 H, CH_3), 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 (EI, 70 eV): m/z (%) = 211 (77) [M^+], 170 (93), 105 (100).

UV (MeOH): λ_{max}(log ε) = 207 nm (4.646), 264 (4.172), 298 (sh, 4.397).

Anal. Calcd for $C_8H_9N_3O_2S$ (211.25): C, 45.5; H, 4.29; N, 19.89. Found: C, 45.6; H, 4.32; N, 19.96.

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