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Hetero-Diels–Alder reaction of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with arylsulfonylcyanides. Synthesis and antimicrobial activity of 4-hydroxy-2-(arylsulfonyl)pyridines

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ABSTRACT

Hetero-Diels–Alder reactions of 1,3-bis(silyloxy)-1,3-butadienes with arylsulfonylcyanides afforded a variety of 4-hydroxy-2-(arylsulfonyl)pyridines. Several derivatives show antimicrobial activity against Gram-positive bacteria.

1. Introduction

Nitriles represent versatile electrophilic building blocks in base-mediated cyclization reactions with nucleophiles.[1,2] In contrast, cycloaddition reactions of nitriles are more rare.[1] Known examples include, for example, transition metal-catalyzed [2 + 2 + 2] cycloaddition of nitriles with two molecules of alkynes.[3] The photochemical [2 + 2] cycloaddition of aryl nitriles with electron rich alkenes has been reported to give azetines.[4a–c] A 1,3-azetin-2-one has been prepared by [2 + 2] cycloaddition of trichloroacetylisocyanate with trichloroacetonitrile.[4d] The [3 + 2] cycloaddition of nitriles with azides has been reported to give 1*H*-tetrazoles.[5] The best yields were generally obtained for nitriles containing an electron deficient substituent. Sharpless et al. studied the synthesis of tetrazoles by Cu-catalyzed 'click reaction' of nitriles with azides.[6] For example, 1-substituted-5-tosyltetrazoles were prepared from tosyl cyanide (TsCN); the tosyl group was subsequently elaborated by nucleophilic substitution reactions. The 1,3-dipolar cycloaddition of diazomethane with TsCN has been reported to give 1,2,3-triazines.[7]

The [4 + 2] cycloaddition of nitriles with 1,3-dienes (hetero-Diels–Alder reaction) has been reported to give dihydropyridines which often undergo elimination or oxidation reactions to the corresponding pyridine derivatives. Noteworthy, intermolecular reactions of this type are relatively rare and highly activated nitriles, such as arylsulfonylnitriles and cyanoformates, have to be employed.[8] Breitmaier and Rüffer reported[8f] an efficient synthesis of functionalized pyridines by cyclization of 1,3-butadienes, including 2-silyloxy-1,3-butadienes, with tosylcyanide[9] (TsCN). Pyridines have been prepared also by cyclization of pyran-2-ones with TsCN with extrusion of carbon dioxide.[10] Recently, the synthesis of 1-azabicyclo[2.2.2]oct-1-enes by cyclization of 2-silyloxycyclohexa-1,3-diene with TsCN has been reported.[11] Recently, we reported,[12] based on the work of Breitmaier, the hetero-Diels–Alder reaction of 1,3-bis(trimethylsilyloxy)-1,3-butadienes[13] with TsCN. Herein, we report full details of these studies and a considerable extension of the scope. The reactions reported herein allow a convenient synthesis of a variety of functionalized 4-hydroxy-2-(arylsulfonyl)pyridines which are not readily available by other methods.

In recent years, it has been shown that 2-(arylsulfonyl)pyridines and related molecules are of considerable pharmacological relevance. 10-Oxa-9-thia-1-aza-anthracene-9,9-dioxide possesses in vitro (rat brain homogenate) inhibitory activity against monoamine oxidase (MAO).[14] 6-(Benzenesulfonyl)-pyrido[3,2-d]pyrimidine-2,4-diamine shows parenteral antimalarial effects against *Plasmodium Berghi* in mice.[15] 1-(10,10-Dioxo-5λ[9]-dihydro-10,6-thiochromeno[2,3-*b*]pyridin-5-yl)-1,3-dimethyl-urea shows gas-

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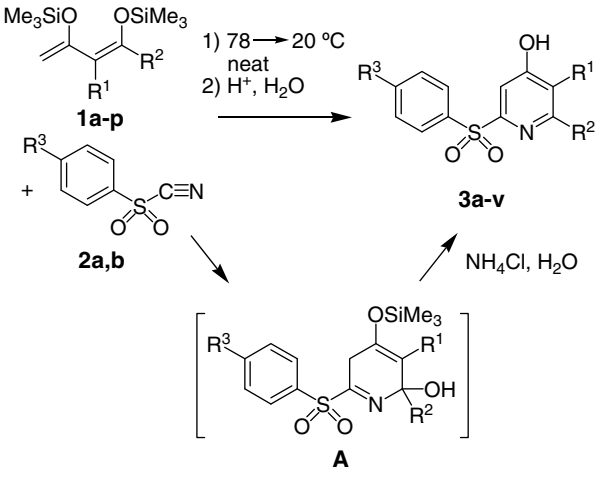
tric antisecretory activity.[16] 2-Benzenesulfonyl-4-methylbenzo[h]quinolines show antibiotic activity against various pathogens.[17] 6-(Benzenesulfonyl)-pyrido[3,2-*d*]pyrimidine-2,4-diamines have been reported to inhibit *Pneumocystis carinii* dihydrofolate reductase and *Toxoplasma gondii* dihydrofolate reductase.[18] 3-[5-(Phenylcarbamoyl)-pyridine-2-sulfonyl]-benzoic acids show binding activity to Sf9 cell membranes.[19] 2,4-Diamino-10,10-dioxo-5,10-dihydro-10λ^6-thiochromeno[2,3-*b*]pyridine-3-carbonitrile and related derivatives inhibit recombinant MAP kinase-activated protein kinase 2.[20] 2-(Benzenesulfonyl)-5-nitropyridines and related compounds show inhibitory activity of recombinant SARS coronavirus main protease 2.[21] 2-(4-Fluoro-benzenesulfonyl)-5-[(E)-2-(4-fluoro-phenyl)-vinyl]-pyridine binds to the human 5-HT2A receptor.[22] Other derivatives have been shown to bind to the human cannabinoid CB2 receptor.[23] Other effects have also been reported.[24] Herein, we report the antimicrobial activity of several 2-(arylsulfonyl)-4-hydroxypyridines prepared by our new synthetic methodology.

2. Results and discussion

The reaction of 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-butadiene (**1a**), readily available from methyl acetoacetate,[25] with *p*-toluenesulfonyl cyanide (TsCN, **2a**) afforded the 4-hydroxy-2-tosylpyridine **3a** in 43% yield (Scheme 1, Table 1). The best yields were obtained when a neat mixture of the starting materials was allowed to slowly warm from −78 °C to ambient temperature. A complex mixture was obtained when the reaction was carried out at elevated temperatures or when a solvent was added. An aqueous work-up using NH_4Cl or HCl was necessary. The formation of **3a** can be explained by [4 + 2] cycloaddition to give intermediate **A** and subsequent acid-mediated cleavage of the silyloxy group and aromatization.

The cyclization of 1,3-bis(silyloxy)-1,3-butadienes **1a**–**p** with arylsulfonyl cyanides **2a**,**b** afforded the 4-hydroxy-2-sulfonylpyridines **3a**–**v** (Table 1). The reaction conditions were optimized. The reactions of dienes **1a**,**b**,**e**,**f**, prepared from unsubstituted β-ketoesters, were carried out at 20 °C (the starting materials were added at −78 °C and the mixture was subsequently warmed to 20 °C during 30 min. The reaction time was in the range of 24–28 h. A considerable extension of the reaction time was necessary for the less reactive dienes **1c** and **1d** derived from pentane-2,4-dione and 1-methoxy-pentane-2,4-dione, respectively. In these cases, the starting materials were added at 0 rather than −78 °C. The reactions were carried out at 20 °C. An increase of the temperature resulted in partial decomposition. The reactions of dienes **1g**–**i** and **1m**–**o** were carried out at 45 °C (48 h). The arylthio-substituted dienes **1j**–**l**,**p** solidify at 20 °C. Since all reactions reported herein had to be carried out without solvent (neat) it proved to be advantageous to carry out the reactions of **1j**–**l**,**p** at 60 °C (96 h).



Scheme 1. Synthesis of **3a**–**v**.

Table 1
Synthesis of **3a**–**v**

1	2	3	R^1	R^2	R^3	% (3)[a]
a	**a**	**a**	H	OMe	Me	43
b	**a**	**b**	H	OEt	Me	30
c	**a**	**c**	H	CH_2OMe	Me	30
d	**a**	**d**	H	Me	Me	33
e	**a**	**e**	H	$O(CH_2)_2OMe$	Me	12
a	**a**	**f**	H	OMe	H	10
b	**b**	**g**	H	OEt	H	38
f	**b**	**h**	H	OiPr	H	31
g	**b**	**i**	Cl	OEt	H	56
h	**b**	**j**	F	OEt	H	59
i	**b**	**k**	$O(3,5\text{-}Me_2C_6H_3)$	OEt	H	61
j	**b**	**l**	SPh	Me	H	53
k	**b**	**m**	SPh	OMe	H	56
l	**b**	**n**	$S(3\text{-}MeC_6H_4)$	Me	H	79
g	**a**	**o**	Cl	OEt	Me	48
h	**a**	**p**	F	OEt	Me	54
m	**b**	**q**	Et	OMe	H	60
n	**a**	**r**	$O(3\text{-}MeC_6H_4)$	Me	Me	58
o	**a**	**s**	$O(4\text{-}MeC_6H_4)$	Me	Me	57
i	**a**	**t**	$O(3,5\text{-}Me_2C_6H_3)$	OEt	Me	62
j	**a**	**u**	SPh	Me	Me	64
p	**a**	**v**	$S(4\text{-}MeC_6H_4)$	Me	Me	51

[a] Yields of isolated products.

Noteworthy, the yields of pyridines **3i**–**v** were considerably higher than those of **3a**–**h**. This can be explained by the *cisoid* conformation of 1,3-bis(silyloxy)-1,3-butadienes **1g**–**s**, due to the presence of the substituent located at the *central* carbon atom. The reaction of **2a** with 1,3-bis(silyloxy)-1,3-butadienes containing a substituent located at the *terminal* carbon atom proved to be unsuccessful, presumably due to steric reasons. The reaction of **1a** with ethoxycarbonyl cyanide was also unsuccessful, due to the low reactivity of the latter compared to **2a**. No conversion was observed when the reaction was carried out at 20 and 60 °C. Forcing conditions (neat, 120 °C) resulted in decomposition and 1,5 O → C TMS shift of the 1,3-bis(silyl enol ether) to give a 3-silyloxy-4-silylcrotonate.[26]

The structures of the products were elucidated by spectroscopic methods (2D NMR). The structures of **3l** and **3r** were independently confirmed by X-ray crystal structure analyses (Figs. 1 and 2).[27]

All arylsulfonyl-pyridines were tested towards their antimicrobial activity. The agar diffusion test method was used to evaluate the influence on the growth of the Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis* as well as the Gram-negative *Escherichia coli* and the yeast *Candida maltosa*. The results of that screening are summarized in Table 2. Some of the compounds showed considerable activities against *S. aureus* and *B. subtilis*. In this screening no activity against the Gram-negative *E. coli* was observed. Only **3o** showed a weak activity against the yeast *C. maltosa*. Compound **3o** is also among the most active derivatives in this study. To evaluate the antimicrobial potential of the most active compounds minimal inhibitory concentrations were determined. The results of these investigations are summarized in Table 3. Derivatives **3i**,**j**,**o**, containing a halogen atom located at the pyridine moiety, show the best activities. A good activity was also observed for derivative **3n** containing a tolylthio moiety.

The chloro derivatives **3i** and **3o** show a good antibiotic activity against the tested Gram-positive pathogenes. Interestingly, the

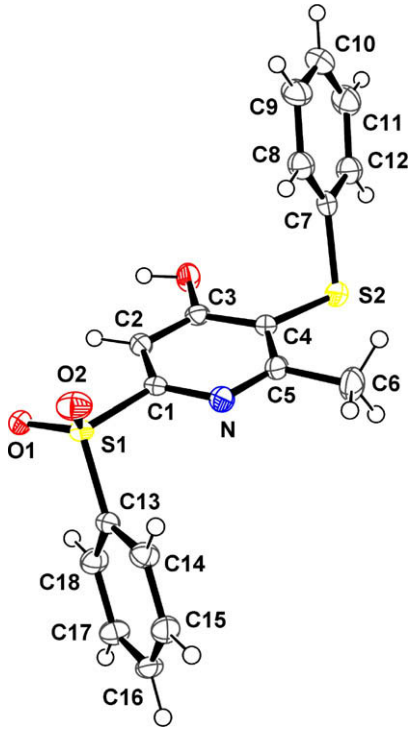


Figure 1. Crystal structure of **3l**.

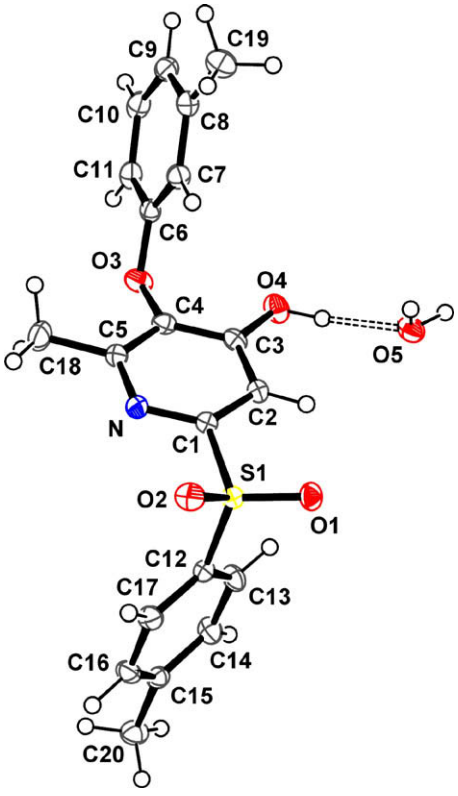


Figure 2. Crystal structure of **3r**.

thio-substituted sulfonyl-pyridines **3l–n** and **3u–v** are also active, but at a lower level in the agar diffusion assay. In contrast to this observation, the MIC of **3n**, **3u** and **3v** are lower compared to the chlorinated compounds **3i** and **3o**. A possible explanation would be a better bioavailability in case of the non-chlorinated derivatives in the dilution assay. All compounds show much lower activity compared to Ampicillin in this study. In future studies, the influence of a halogenation at position R^2 or R^3 in the thioaryl derivatives could be of interest to get better insight into the structure-activity relationships.

Table 2
Results of the antimicrobial screening[a]

3	*S. aureus* ATCC 6538	*B. subtilis* ATCC 6051	*E. coli* ATCC 11229	*C. maltosa* SBUG 700
a	10	r	r	r
b	r	r	r	r
c	r	r	r	r
d	r	r	r	r
e	r	r	r	r
f	r	r	r	r
g	r	r	r	r
h	r	r	r	r
i	12	11	r	r
j	12	11	r	r
k	r	r	r	r
l	9	10	r	r
m	r	10	r	r
n	13	10	r	r
o	13	10	r	9
p	r	8	r	r
q	r	r	r	r
r	r	r	r	r
s	8	7	r	r
t	8	r	r	r
u	r	10	r	r
v	8	10	r	r
Ampicillin	27	25	19	n.t.
Nystatin	n.t.	n.t.	n.t.	28

[a] Inhibition zones are stated in diameter (mm) without the diameter of the paper disc (6 mm); r, resistant; n.t., not tested.

Table 3
Minimal inhibitory concentrations of selected compounds **3** (values give in mM)[a]

3	*S. aureus* ATCC 6538	*B. subtilis* ATCC 6051
i	1.59	1.59
j	3.36	1.68
n	0.67	0.33
o	1.53	1.52
u	0.67	0.34
v	0.32	0.16
Ampicillin	0.003	0.011

[a] Minimal inhibitory concentrations were determined by a dilution assay (results are averages of three independent experiments).

3. Conclusions

In conclusion, the hetero-Diels–Alder reaction of 1,3-bis(silyloxy)-1,3-butadienes with arylsulfonylcyanides afforded a variety of 4-hydroxy-2-(arylsulfonyl)pyridines. The products, which are not readily available by other methods, show a considerable antimicrobial activity against Gram-positive bacteria.

4. Experimental section

4.1. General comments

All solvents were dried by standard methods and all reactions were carried out under an inert atmosphere. For ^1H and ^{13}C NMR spectra the deuterated solvents indicated were used. Mass spectro-

metric data (MS) were obtained by electron ionization (EI, 70 eV), chemical ionization (CI, H_2O) or electrospray ionization (ESI). For preparative scale chromatography, silica gel (60–200 mesh) was used. Melting points are uncorrected.

4.2. General procedure for the synthesis of 2-(arylsulfonyl)-4-hydroxypyridines 3a–v

To the arylsulfonyl cyanide **2** (1.0 equiv) was added dropwise the 1,3-bis(silyl enol ether) **1** (2.0–2.5 equiv) at −78 °C. The neat reaction mixture was allowed to warm 45−60 °C during 48−96 h with stirring. To the mixture was added a saturated aqueous solution of NH_4Cl (20 mL) and the organic and the aqueous layer were separated. The latter was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered and the filtrate was concentrated in vacuo. The residue was purified by chromatography (silica gel, *n*-heptane/EtOAc) to give **3a–v**. The synthesis of **3a–h** has been previously reported in our preliminary communication.[13]

4.3. 3-Chloro-2-ethoxy-6-(phenylsulfonyl)pyridin-4-ol (3i)

Starting with **2a** (0.167 g, 1.0 mmol) and 1 g (0.617 g, 2.0 mmol), **3i** was isolated as a yellow viscous oil (0.175 g, 56%). Reaction conditions: 48 h, 45 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.22 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 4.27 (q, ^3J = 7.1 Hz, 2 H, OCH_2CH_3), 7.19 (s(br), 1 H, OH_{Heter}), 7.44−7.49 (m, 2 H, CH_{Ph}), 7.52 (m, 1 H, CH_{Ph}), 7.55 (s, 1 H, CH_{Heter}), 7.96 (dd, ^3J = 8.4 Hz, ^4J = 1.5 Hz, 2 H, CH_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (OCH_2CH_{3Heter}), 64.1 (OCH_2CH_3), 105.6 (CH_{Heter}), 106.9 (C_{Heter}), 128.9 ($2CH_{Ph}$), 129.0 ($2CH_{Ph}$), 133.8 (CH_{Ph}), 138.4 (C_{Ph}), 153.6 (COH_{Heter}), 159.9, 160.4 (C_{Heter}). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3312 (w), 1731 ((br), w), 1608 (m), 1417 (m), 1385 (m), 1347 (m), 1304 (m), 1251 (m), 1159 (m), 1093 (s), 1076 (s), 840 (s), 725 (s), 592 (s). HRMS (ESI, Positive): Calcd for $C_{13}H_{12}ClNO_4S$ ($[M+H]^+$, ^{35}Cl): 314.02483; found: 314.02486, ($[M+Na]^+$, ^{35}Cl): 336.006433; found: 336.00678.

4.4. 2-Ethoxy-3-fluoro-6-(phenylsulfonyl)pyridin-4-ol (3j)

Starting with **2b** (0.167 g, 1.0 mmol) and 1 h (0.589 g, 2.0 mmol), **3j** was isolated as a red solid (0.179 g, 59%). Reaction conditions: 48 h, 45 °C ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.22 (t, ^3J = 7.1 Hz, 3 H, OCH_2CH_3), 4.26 (q, ^3J = 7.0 Hz, 2 H, OCH_2CH_3), 7.19 (s(br), 1 H, OH_{Heter}), 7.43 (m, 1 H, CH_{Heter}), 7.46−7.50 (m, 2 H, CH_{Ph}), 7.53−7.56 (m, 1 H, CH_{Ph}), 7.95 (dd, ^3J = 8.4 Hz, ^4J = 1.5 Hz, 2 H, CH_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (OCH_2CH_3), 63.6 (OCH_2CH_3), 107.8 (CH_{Heter}), 128.9 ($2CH_{Ph}$), 129.0 ($2CH_{Ph}$), 133.8 (CH_{Ph}), 136.8 (d, ^1J = 252.4 Hz, CF_{Heter}), 138.4 (C_{Ph}), 149.4 (d, ^4J = 6.7 Hz, C_{Heter}), 151.3 (d, ^2J = 10.2 Hz, COH_{Heter}), 153.8 (d, ^2J = 9.9 Hz, C_{Heter}). ^{19}F NMR (235 MHz, $CDCl_3$): −162.05 (CF_{Heter}). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3354 (w), 1576 (m), 1440 (m), 1353 (m), 1317 (m), 1149 (s), 1076 (m), 1022 (m), 740 (s), 724 (s), 682 (s), 585 (s). HRMS (ESI, Positive): Calcd for $C_{13}H_{12}FNO_4S$ ($[M+H]^+$): 298.05438; found: 298.05413, ([M+Na): 320.03652; found: 320.03633.

4.5. 3-(3,5-Dimethylphenoxy)-2-ethoxy-6-(phenylsulfonyl)pyridin-4-ol (3k)

Starting with **2b** (0.167 g, 1.0 mmol) and **1i** (0.756 g, 2.0 mmol), 3 k was isolated as yellow viscous oil (0.243 g, 61%). Reaction conditions: 48 h, 45 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.99 (t, ^3J = 7.0 Hz, 3 H, OCH_2CH_3), 2.14 (s, 6 H, CH_{3Xyl}), 4.16 (q, ^3J = 7.0 Hz, 2 H, OCH_2CH_3), 6.37 (s, 2 H, CH_{Xyl}), 6.59 (s, 1 H, CH_{Xyl}), 6.77 (s(br), 1 H, OH_{Heterl}), 7.45−7.48 (m, 2 H, CH_{Ph}), 7.48 (s, 1 H, CH_{Heter}), 7.51 (m, 1 H, CH_{Ph}), 7.98 (dd, ^3J = 8.5 Hz, ^4J = 1.5 Hz, 2 H, CH_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.1 (OCH_2CH_3), 19.3 ($2CH_{3Xyl}$), 61.2 (OCH_2CH_3), 104.8 (CH_{Heter}), 111.1 ($2CH_{Ph}$), 122.9 (CH_{Xyl}), 125.9 (C_{Heter}), 126.9 ($2CH_{Ph}$), 127.1 ($2CH_{Xyl}$), 131.7 (CH_{Ph}), 136.7 (C_{Xyl}), 137.5 (C_{Ph}), 148.8 ($2C_{Xyl}$), 154.5 (COH_{Heter}), 155.1, 155.6 (C_{Heter}). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3324 (w), 1592 (s), 1468 (m), 1429 (m), 1305 (m), 1132 (s), 1095 (m), 997 (m), 831 (m), 724 (s), 679 (s), 594 (s). HRMS (ESI, Positive): Calcd for $C_{21}H_{21}NO_5S$ ($[M+H]^+$): 400.12132; found: 400.12108, ($[M+Na]^+$): 422.10299; found: 422.10326.

4.6. 2-Methyl-6-(phenylsulfonyl)-3-(phenylthio)pyridin-4-ol (3l)

Starting with **2b** (0.167 g, 1.0 mmol) and **1j** (0.704 g, 2.0 mmol), **3l** was isolated as a yellow viscous oil (0.189 g, 53%). Reaction conditions: 96 h, 60 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.46 (s, 3 H, CH_{3Heter}), 6.89 (dd, ^3J = 8.2 Hz, ^4J = 1.9 Hz, 2 H, CH_{Tol}), 7.10 (m, 3 H, CH_{Tol}), 7.38 (s(br), 1 H, OH_{Heter}), 7.47 (m, 3 H, CH_{Tol}), 7.59 (s, 1 H, CH_{Heter}), 7.95 (dd, ^3J = 8.4 Hz, ^4J = 1.5 Hz, 2 H, CH_{Tol}). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 20.4 (CH_{3Heter}), 108.17 (CH_{Heter}), 117.7 (C_{Ph}), 126.1 (C_{Heter}), 127.1 ($2CH_{Ph}$), 129.1 ($2CH_{Ph}$), 129.6 ($2CH_{Ph}$), 129.9 ($2CH_{Ph}$), 133.9 ($2CH_{Ph}$), 138.5 (C_{Ph}), 159.1, 165.5 (C_{Heter}), 165.6 (COH_{Heter}). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3249 (w), 1562 (m), 1446 (m), 1397 (m), 1307 (m), 1156 (s), 1082 (m), 905 (s), 721 (s), 684 (m), 601 (s). GC–MS (EI, 70 eV): *m/z* (%) = 357 ($[M]^+$, 4), 292 (100), 252 (4), 216 (6), 147 (6), 109 (24), 77 (19), 65 (7), 51 (10). HRMS (EI): Calcd for $C_{18}H_{15}NO_3S_2$: 357.04879; found: 357.04863.

4.7. 2-Methoxy-6-(phenylsulfonyl)-3-(phenylthio)pyridin-4-ol (3m)

Starting with **2b** (0.167 g, 1.0 mmol) and 1 k (0.746 g, 2.0 mmol), **3m** was isolated as a yellow solid (0.210 g, 56%). Reaction conditions: 96 h, 60 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.73 (s, 3 H, OCH_{3Heter}), 7.02 (m, 1 H, CH_{Ph}), 7.05 (m, 1 H, CH_{Ph}), 7.15 (m, 2 H, CH_{Ph}), 7.18 (m, 2 H, CH_{Ph}), 7.45 (s, 1 H, CH_{Heter}), 7.47 (m, 1 H, CH_{Heter}), 7.50 (s(br), 1 H, OH_{Heter}), 7.54−7.57 (m, 1 H, CH_{Ph}), 8.01 (d, ^3J = 6.9 Hz, 2 H, CH_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 55.1 (OCH_{3Heter}), 104.7 (CH_{Heter}), 125.2 (C_{Heter}), 127.1 (CH_{Ph}), 128.1 ($2CH_{Ph}$), 125.9 ($2CH_{Ph}$), 129.2 ($2CH_{Ph}$), 129.3 ($2CH_{Ph}$), 132.6, 137.3 (C_{Ph}), 133.8 (CH_{Ph}), 138.3 (C_{Ph}), 157.4 (COH_{Heter}), 164.9, 166.5 (C_{Heter}). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3246 (w), 1625 (m), 1559 (w), 1503 (m), 1445 (m), 1385 (m), 1301 (s), 1142 (s), 1076 (s), 906 (m), 724 (s), 600 (s). HRMS (ESI, Positive): Calcd for $C_{18}H_{15}NO_4S_2$ ($[M+H]^+$): 374.05153; found: 374.05163, ($[M+Na]^+$): 396.03360; found: 396.03347.

4.8. 2-Methyl-6-(phenylsulfonyl)-3-(*m*-tolylthio)pyridin-4-ol (3n)

Starting with **2b** (0.167 g, 1.0 mmol) and **1l** (0.733 g, 2.0 mmol), **3n** was isolated as a yellow viscous oil (0.296 g, 79%). Reaction conditions: 96 h, 60 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.20 (s, 3 H, CH_{3Tol}), 2.48 (s, 3 H, CH_3, CH_{3Heter}), 6.82 (d, ^3J = 8.2 Hz, 2 H, CH_{Tol}), 6.98 (d, ^3J = 8.1 Hz, 1 H, CH_{Ph}), 7.45 (m, 1 H, CH_{Tol}), 7.48 (m, 1 H, CH_{Ph}), 7.55 (s(br), 1 H, OH_{Heter}), 7.63 (m, 1 H, CH_{Heter}), 7.52 (m, 1 H, CH_{Tol}), 8.00 (dd, ^3J = 8.1 Hz, ^4J = 1.5 Hz, 1 H, CH_{Ph}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9 (CH_{3Tol}), 21.9 (CH_{3Heter}), 105.9 (CH_{Heter}), 113.2, 116.3 (C_{Heter}), 126.0 ($2CH_{Ph}$), 126.7 (CH_{Tol}), 127.1 ($2CH_{Tol}$), 127.2 (CH_{Tol}), 127.9 (C_{Ph}), 128.4 ($2CH_{Ph}$), 131.8 (CH_{Ph}), 135.5 (C_{Tol}), 136.6 (C_{Tol}), 157.0 (COH_{Heter}), 163.4 (C_{Heter}). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3377 (w), 2921 (w), 1561 (m), 1491 (m), 1446 (m), 1396 (m), 1306 (m), 1155 (s), 1081 (m), 1015 (w), 905 (s), 803 (m), 722 (s), 684 (m), 600 (s). GC–MS (CI, Positive, 70 eV): *m/z* (%) = 371 ($[M]^+$, 14), 306 (100), 292 (5), 274 (4), 216 (5), 186 (3), 135 (6), 123

(27), 91 (8), 77 (24), 65 (4), 45 (7). HRMS (EI): Calcd for $C_{19}H_{17}NO_3S_2$ ([M]$^+$): 371.06444; found: 371.06407.

4.9. 3-Chloro-2-ethoxy-6-tosylpyridin-4-ol (3o)

Starting with **2a** (0.094 g, 1.0 mmol) and 1 g (0.617 g, 2.0 mmol), **3o** was isolated as a red viscous oil (0.156 g, 48%). Reaction conditions: 48 h, 45 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (t, ^3J = 7.8 Hz, 3 H, OCH_2CH_3), 2.35 (s, 3 H, CH_{3Tol}), 4.28 (q, ^3J = 6.8 Hz, 2 H, OCH_2CH_3), 7.19 (s, 1 H, CH_{Heter}), 7.24 (d, ^3J = 8.1 Hz, 2 H, CH_{Tol}), 7.42 (s(br), 1 H, OH_{Heterl}), 7.84 (d, ^3J = 8.2 Hz, 2 H, CH_{Tol}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (OCH_2CH_{3Heter}), 21.6 (CH_{3Tol}), 64.0 (OCH_2CH_3), 105.4 (CH_{Heter}), 106.7 (C_{Heter}), 129.1 ($2CH_{Tol}$), 129.6 ($2CH_{Tol}$), 135.5, 144.8 (C_{Tol}), 153.9 (COH_{Heter}), 159.8, 160.3 (C_{Heter}). IR (neat, cm^{-1}): $\tilde{\nu}$ = 2952 (w), 1594 (m), 1415 (m), 1338 (m), 1252 (m), 1115 (s), 1078 (s), 840 (s), 676 (s), 589 (s). MS (CI, Positive, 70 eV): *m/z* (%) = 330 ([M+1]$^+$, ^{37}Cl, 35), 328 ([M+1]$^+$, ^{35}Cl, 100), 299 (4), 279 (2), 257 (5), 233 (3), 219 (3), 193 (3), 177 (4), 141 (5), 125 (5), 81 (^{37}Cl, 11), 79 (^{35}Cl, 97), 71 (17). HRMS (ESI, Positive): Calcd for $C_{14}H_{14}ClNO_4S$ ([M+H]$^+$, ^{35}Cl): 328.04048; found: 328.04058, ([M+Na]$^+$, ^{35}Cl): 350.02243; found: 350.0039.

4.10. 2-Ethoxy-3-fluoro-6-tosylpyridin-4-ol (3p)

Starting with **2a** (0.188 g, 1.0 mmol) and 1 h (0.589 g, 2.0 mmol), **3p** was isolated as a red viscous oil (0.178 g, 54%). Reaction conditions: 48 h, 45 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.24 (t, ^3J = 6.8 Hz, 3 H, OCH_2CH_3), 2.35 (s, 3 H, CH_{3Tol}), 4.27 (q, ^3J = 6.8 Hz, 2 H, OCH_2CH_3), 7.23 (s(br), 1 H, OH_{Heter}), 7.27 (d, ^3J = 8.1 Hz, 2 H, CH_{Tol}), 7.46 ($d_{H,\ F}$, ^4J = 5.0 Hz, 1 H, CH_{Heter}), 7.82 (d, ^3J = 8.5 Hz, 2 H, CH_{Tol}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (OCH_2CH_3), 21.6 (CH_{3Tol}), 63.5 (OCH_2CH_3), 107.6 (CH_{Heter}), 128.9 ($2CH_{Tol}$), 129.6 ($2CH_{Tol}$), 135.5 (C_{Tol}), 137.8 (d, ^1J = 251.9 Hz, CF_{Heter}), 144.8 (C_{Tol}), 149.7 (d, ^4J = 6.2 Hz, C_{Heter}), 151.3 (d, ^2J = 9.9 Hz, COH_{Heter}), 153.7 (d, ^2J = 9.9 Hz, C_{Heter}). ^{19}F NMR (235 MHz, $CDCl_3$): −162.63 (CFHeter). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3255 (w), 1624 (m), 1505 (m), 1425 (m), 1383 (m), 1261 (s), 1140 (m), 1084 (m), 811 (m), 686 (m), 600 (m). MS (CI, Positive, 70 eV): *m/z* (%) = 312 ([M+1]$^+$, 100), 247 (8), 219 (6), 177 (3), 119 (11), 69 (7). HRMS (ESI, Positive): Calcd for $C_{14}H_{14}FNO_4S$ ([M+H]$^+$): 312.07003; found: 312.06950, ([M+Na]$^+$): 334.05198; found: 334.05194.

4.11. 3-Ethyl-2-methoxy-6-(phenylsulfonyl)pyridin-4-ol (3q)

Starting with **2b** (0.188 g, 1.0 mmol) and 1 m (0.576 g, 2.0 mmol), **3q** was isolated as a yellow viscous oil (0.176 g, 60%). Reaction conditions: 48 h, 45 °C. ^{1}H NMR (250 MHz, CD_3OD): δ = 0.97 (t, ^3J = 7.9 Hz, 3 H, CH_2CH_3), 2.46 (q, ^3J = 7.7 Hz, 2 H, CH_2CH_3), 3.24 (s, 3 H, OCH_{3Heter}), 6.97 (s, 1 H, CH_{Heter}), 7.32−7.35 (m, 3 H, CH_{Ph}), 7.78 (d, ^3J = 9.8 Hz, 2 H, CH_{Ph}). ^{13}C NMR (75 MHz, CD_3OD): δ = 12.7 (CH_2CH_3), 17.3 (CH_2CH_3), 50.0 (OCH_{3Heter}), 104.9 (CH_{Heter}), 118.1 (C_{Heter}), 129.5 ($2CH_{Ph}$), 130.9 ($2CH_{Ph}$), 137.7 (CH_{Ph}), 146.5 (C_{Ph}), 151.5 (COH_{Heter}), 164.7, 165.3 (C_{Heter}). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3417 (w), 2933 (w), 1726 (m), 1613 (m), 1413 (m), 1319 (s), 1267 (s), 1146 (s), 1083 (s), 904 (w), 812 (m), 674 (s), 592 (s). MS (EI, 70 eV): *m/z* (%) = 293 ([M]$^+$, 100), 229 (96), 186 (8), 160 (14), 139 (64), 91 (37), 69 (26). HRMS (ESI, Positive): Calcd for $C_{14}H_{15}NO_4S$ ([M+H]$^+$): 294.07946; found: 294.07964, ([M+Na]$^+$): 316.06140; found: 316.06148.

4.12. 2-Methyl-3-(*m*-tolyloxy)-6-tosylpyridin-4-ol (3r)

Starting with **2a** (0.141 g, 0.750 mmol) and **1n** (0.525 g, 1.5 mmol), **3r** was isolated as colorless solid (0.240 g, 58%). Reaction conditions: 48 h, 45 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.16 (s, 3 H, CH_{3Tol}), 2.18 (s, 3 H, CH_{3Tol}), 2.32 (s, 3 H, CH_{3Heter}), 6.47 (m, 1 H, CH_{Tol}), 6.53 (s, 1 H, CH_{Heter}), 6.75 (d, ^3J = 7.3 Hz, 1 H, CH_{Tol}), 7.00−7.06 (m, 2 H, CH_{Tol}), 7.21 (d, ^3J = 8.2 Hz, 2 H, CH_{Tol}), 7.62 (s(br), 1 H, OH_{Heter}), 7.82 (d, ^3J = 8.2 Hz, 2 H, CH_{Tol}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.1 (CH_{3Heter}), 19.4, 19.7 (CH_{3Tol}), 108.9 (CH_{Heter}), 109.9, 113.6, 121.9 (CH_{Tol}), 126.9 ($2CH_{Tol}$), 127.5 (CH_{Tol}), 127.8 ($2CH_{Tol}$), 133.9, 137.8 (C_{Tol}), 138.2 (C_{Heter}), 142.9 (C_{Tol}), 152.2 (C_{Heter}), 152.6 (C_{Tol}), 154.3 (COH_{Heter}), 179.3 (C_{Heter}). GC–MS (CI, Positive, 70 eV): *m/z* (%) = 370 ([M+1]$^+$, 100), 305 (58), 291 (4), 232 (8), 69 (24). HRMS (ESI, Positive): Calcd for $C_{20}H_{19}NO_4S$ ([M+H]$^+$): 370.11076; found: 370.11067, ([M+Na]$^+$): 392.09270; found: 392.09270.

4.13. 2-Methyl-3-(*p*-tolyloxy)-6-tosylpyridin-4-ol (3s)

Starting with **2a** (0.141 g, 0.75 mmol) and **1o** (0.525 g, 1.75 mmol), **3s** was isolated as a yellow solid (0.210 g, 57%). Reaction conditions: 48 h, 45 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_{3Tol}), 2.21 (s, 3 H, CH_{3Tol}), 2.34 (s, 3 H, CH_{3Heter}), 6.61 (d, ^3J = 8.5 Hz, 2 H, CH_{Tol}), 6.98 (d, ^3J = 8.3 Hz, 2 H, CH_{Tol}), 7.19 (s, 1 H, CH_{Heter}), 7.24 (d, ^3J = 8.1 Hz, 2 H, CH_{Tol}), 7.64 (s(br), 1 H, OH_{Heter}), 7.86 (d, ^3J = 8.2 Hz, 2 H, CH_{Tol}). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 21.6 (CH_{3Tol}), 30.9 (CH_{3Heter}), 110.3 (CH_{Heter}), 113.8 (C_{Tol}), 114.7 ($2CH_{Tol}$), 128.9 ($2CH_{Tol}$), 129.7 ($2CH_{Tol}$), 129.9 (C_{Tol}), 130.4 ($2CH_{Tol}$), 130.7 (C_{Tol}), 132.7, 136.0, 139.6 (C_{Heter}), 144.7 (C_{Tol}), 154.7 (COH_{Heter}). MS (EI, 70 eV): *m/z* (%) = 369 ([M]$^+$, 1), 320 (1), 305 (100), 288 (10), 214 (13), 186 (9), 139 (8), 107 (9), 91 (45), 65 (16). HRMS (ESI): Calcd for $C_{20}H_{19}NO_4S$ ([M+1]$^+$): 370.11076; found: 370.11067, ([M+Na]$^+$): 392.09270; found: 392.09732.

4.14. 3-(3,5-Dimethylphenoxy)-2-ethoxy-6-tosylpyridin-4-ol (3t)

Starting with **2a** (0.188 g, 1.0 mmol) and **1i** (0.757 g, 2.0 mmol), **3t** was isolated as a red viscous oil (0.253 g, 62%). Reaction conditions: 48 h, 45 °C. ^{1}H NMR (250 MHz, CD_3OD): δ = 0.97 (t, ^3J = 7.3 Hz, 3 H, OCH_2CH_3), 2.29 (s, 6 H, CH_{3Xyl}), 2.52 (s, 3 H, CH_{3Tol}), 4.28 (q, ^3J = 7.4 Hz, 2 H, OCH_2CH_3), 6.54 (s, 2 H, CH_{Xyl}), 6.72 (s, 1 H, CH_{Xyl}), 7.26 (s, 1 H, CH_{Heterl}), 7.51 (d, ^3J = 8.0 Hz, 2 H, CH_{Tol}), 8.01 (d, ^3J = 8.3 Hz, 2 H, CH_{Tol}). ^{13}C NMR (75 MHz, CD_3OD): δ = 14.2 (OCH_2CH_{3Heter}), 21.3 ($2CH_{3Xyl}$), 21.4 (CH_{3Tol}), 62.7 (OCH_2CH_{3Heter}), 106.7 (CH_{Heter}), 113.8 ($2CH_{Xyl}$), 124.9 (CH_{Xyl}), 129.6 ($2CH_{Tol}$), 131.0 ($2CH_{Tol}$), 140.3 (C_{Tol}), 143.3 ($2C_{Xyl}$), 149.6 (C_{Tol}), 158.4 (C_{Heter}), 159.7 (C_{Xyl}), 159.9, 160.4 (C_{Heter}), 170.8 (COH_{Heter}). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3248 (w), 2952 (w), 1632 (s), 1436 (m), 1309 (m), 1178 (s), 1092 (m), 1035 (m), 952 (w), 805 (s), 696 (s). HRMS (ESI): Calcd for $C_{20}H_{19}NO_4S$ ([M+1]$^+$): 414.13784; found: 414.13769, ([M+Na]$^+$): 436.47982; found: 436.47842.

4.15. 2-Methyl-3-(phenylthio)-6-tosylpyridin-4-ol (3u)

Starting with **2a** (0.188 g, 1.0 mmol) and **1j** (0.705 g, 2.0 mmol), **3u** was isolated as colorless oil (0.240 g, 64%). Reaction conditions: 96 h, 60 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.27 (s, 3 H, CH_{3Tol}), 2.41 (s, 3 H, CH_{3Heter}), 6.80 (d, ^3J = 8.2 Hz, 2 H, CH_{Tol}), 7.02−7.06 (m, 3 H, CH_{Ph}), 7.09 (s(br), 1 H, OH_{Heter}), 7.18 (d, ^3J = 8.0 Hz, 2 H, CH_{Ph}), 7.55 (s, 1 H, CH_{Heter}), 7.82 (d, ^3J = 8.3 Hz, 2 H, CH_{Tol}). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 21.6 (CH_{3Tol}), 23.7 (CH_{3Heter}), 108.1 (CH_{Heter}), 117.7 (C_{Ph}), 126.9 (CH_{Ph}), 127.3 ($2CH_{Tol}$), 129.1 ($2CH_{Ph}$), 129.5 ($2CH_{Ph}$), 129.8 ($2CH_{Tol}$), 132.7 (C_{Tol}), 135.5 (C_{Heter}), 145.1 (C_{Tol}), 159.2 (COH_{Heter}), 165.3, 165.8 (C_{Heter}). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3057 (w), 1552 (w), 1396 (m), 1316 (m), 1152 (s), 1081 (s), 905 (m), 728 (s), 678 (s), 590 (s). GC–MS (EI, 70 eV): *m/z* (%) = 371 ([M]$^+$, 1), 306 (100), 292 (3), 266 (6), 230 (4), 214 (3), 190 (4), 147 (5), 109 (22), 91 (17), 77 (6), 65 (14). HRMS (EI): Calcd for $C_{19}H_{17}NO_3S_2$: 371.06444; found: 371.06400.

4.16. 2-Methyl-3-(*p*-tolylthio)-6-tosylpyridin-4-ol (3v)

Starting with **2a** (0.188 g, 1.0 mmol) and **1p** (0.733 g, 2.0 mmol), **3v** was isolated as colorless oil (0.200 g, 51%). Reaction conditions: 96 h, 60 °C. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.17 (s, 3 H, CH_{3Tol}), 2.31 (s, 3 H, CH_{3Tol}), 2.45 (s, 3 H, CH_{3Heter}), 6.85 (d, ^3J = 8.2 Hz, 2 H, CH_{Tol}), 6.94 (d, ^3J = 8.1 Hz, 2 H, CH_{Tol}), 7.22 (d, ^3J = 8.0 Hz, 2 H, CH_{Tol}), 7.60 (s, 1 H, CH_{Heter}), 7.76 (s(br), 1 H, OH_{Heter}), 7.85 (d, ^3J = 8.2 Hz, 2 H, CH_{Tol}). ^{13}C NMR (62 MHz, $CDCl_3$): δ = 20.9, 21.6 (CH_{3Tol}), 23.9 (CH_{3Heter}), 107.7 (CH_{Heter}), 118.0 (C_{Tol}), 127.9 ($2CH_{Tol}$), 128.8 ($2CH_{Tol}$), 129.1 ($2CH_{Tol}$), 129.7 ($2CH_{Tol}$), 135.6, 137.3 (C_{Tol}), 130.7 (C_{Tol}), 144.8, 159.5, 165.1 (C_{Heter}), 165.4 (COH_{Heter}). IR (neat, cm^{-1}): $\tilde{\nu}$ = 3279 (w), 1583 (m), 1546 (m), 1490 (m), 1393 (m), 1306 (m), 1154 (s), 1124 (s), 1076 (s), 964 (w), 799 (s), 680 (s). MS (EI, 70 eV): *m/z* (%) = 385 ([M]$^+$, 13), 320 (100), 306 (7), 280 (11), 228 (11), 160 (6), 135 (10), 123 (45), 91 (38), 79 (12), 65 (9), 45 (13). HRMS (EI): Calcd for $C_{20}H_{19}NO_3S_2$: 385.08009; found: 385.07955.

4.17. Antimicrobial screening

The bacterial cultures were obtained from the ATCC. Assay for antimicrobial activity: a modified disc diffusion method was used to determine the antimicrobial activity. A sterile filter disc of 6 mm diameter (B & D research) was impregnated with the test compounds. The amount of the compounds tested in these experiments was 1 μmol per paper disc. The paper disc was placed on the agar plate seeded with respective microorganisms. The plates were kept in the refrigerator at 4 °C for 4 h. The plates were then turned over to incubate overnight at 37 °C (at 25 °C in case of *C. maltosa*) in an inverted position. At the end of the incubation period the clear zones of inhibition around the paper disc were measured. Negative control experiments were performed by using paper discs loaded with an equivalent volume of solvent, and positive control experiments were performed by the use of an equivalent amount of Ampicillin (in the case of *S. aureus*, *B. subtilis* and *E. coli*) and Nystatin (*C. maltosa*). All experiments were done in triplicate.

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References and notes

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27. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-686724 (**3l**) and CCDC-686725 (**3r**). Copies of this data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk) or via www.ccdc.cam.ac.uk/conts/retrieving.html.