Synthesis of 3-Sulfonyloxypyridines: Oxidative Ring Expansion of α-Furylsulfonamides and N→O Sulfonyl Transfer

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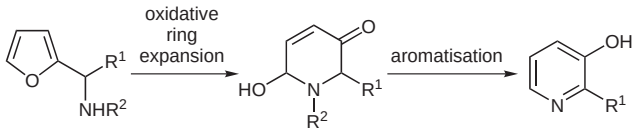
Abstract: *N*-Sulfonyl pyridinones derived from α-furylsulfonamides may be aromatised with concomitant N→O sulfonyl transfer to produce 3-sulfonyloxypyridines.

Key words: furans, pyridines, rearrangements, ring expansion, sulfonamides

The pyridine motif is found in a wide range of biologically active compounds including pyridoxal, niacin and the stimulant, nicotine.[1] Furthermore, many substituted pyridines have been marketed as pharmaceuticals, for example the tuberculosis treatment isoniazid[2a] and the HIV protease inhibitor indinavir.[2b]

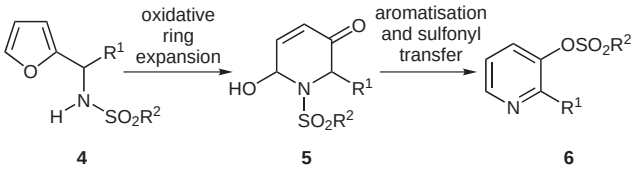
Many differentially substituted pyridines are difficult to prepare. 2,3-Disubstituted pyridines have been synthesised by directed metalation,[3] condensation,[4] nucleophilic addition to pyridinium salts[5] and [2,3]-sigmatropic rearrangement.[6] A p38 MAP kinase inhibitor has been prepared by Pd-catalysed annelation of a 2-chloro 3-iodo 4-bromo pyridine.[7] A remarkable cascade reaction has recently been developed for the synthesis of pentasubstituted pyridines.[8]

An alternative approach involves oxidative ring expansion of an α-furyl amine (e.g. **1** → **2**), and subsequent acid-catalysed aromatisation (→ **3**, Scheme 1).[9] This approach has been applied in the synthesis of *C*-nucleosides[10] and pyridine-substituted sugar mimetics.[11]



Scheme 1

In this paper we describe the development of an oxidative cascade, in which oxidative ring expansion of an α-furyl sulfonamide (e.g. **4**), acid-catalysed aromatisation and N→O sulfonyl transfer leads to the formation of 3-sulfonyloxypyridines such as **6** (Scheme 2). The optimisation

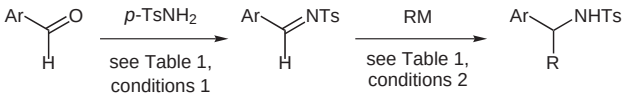


Scheme 2

of this process,[12] and its scope and limitiations, are described. Aryl toluenesulfonates are valuable precursors of highly substituted arenes.[13]

The α-furylsulfonamides **9** were synthesised in two steps from simple aromatic aldehydes (Scheme 3). Treatment of the aldehydes **7** with *p*-toluenesulfonamide in the presence of either tetraethylorthosilicate or titanium(IV) ethoxide gave the *N*-sulfonyl imines **8** (Scheme 3 and Table 1);[14] addition of appropriate organometallic reagents to these imines gave the sulfonamides **9** (Scheme 3 and Table 1).[15]

Treatment of the sulfonamide **9a** with MCPBA or NBS gave the pyridinone **10a** in 99% yield (Scheme 4). Previous aromatisations of pyridinones have used acid catalysis to promote dehydration and, hence, aromatisation.[9,10] We investigated the aromatisation of the pyridinone **10a** in the presence of a range of Lewis acids (Scheme 4); selected examples are described in Table 2. The yield of the pyridine **11a** increased with the strength of the Lewis acid (for example, compare entries 1, 3 and 7). Further optimisation was highly successful: exposure of the pyridinone **10a** to aluminium trichloride in CH_2Cl_2 at –78 °C, and addition of triethylamine, gave the pyridine **11a** in 92% yield (entry 9). In contrast, treatment of the pyridinone **10a** with boron trifluoride, followed by addition of methanol, gave the 3-hydroxypyridine **12** in 72% yield (entry



7a: Ar = 2-Fu
7b: Ar = Ph
7c: Ar = 2-(5-Me)Fu

8a: Ar = 2-Fu
8b: Ar = Ph
8c: Ar = 2-(5-Me)Fu

9a: Ar = 2-Fu, R = ^{n}Bu
9b: Ar = 2-Fu, R = ^{i}Pr
9c: Ar = Ph, R = 2-Fu
9d: Ar = R = 2-Fu
9e: Ar = 2-(5-Me)Fu, R = ^{n}Bu

Fu = furyl

Scheme 3 Preparation of α-furylsulfonamides

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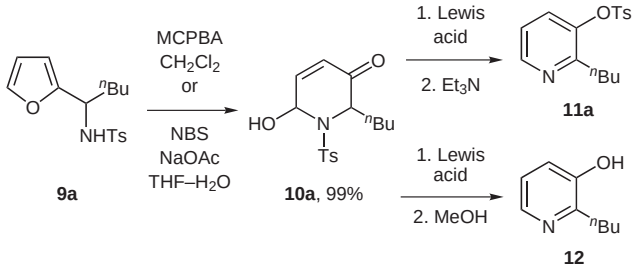
Table 1 Preparation of the α-Furylsulfonamides **9a–e**

Entry	Aldehyde	Conditions 1	Yield (%)	Imine	Conditions 2	Product	Yield (%)
1	**7a**	$Ti(OEt)_4$, CH_2Cl_2, 50 °C	95	**8a**	*n*-BuLi, THF, –78 °C	**9a**	88
2				**8a**	*i*-PrMgCl, THF, –78 °C	**9b**	21
3	**7b**	$Si(OEt)_4$, 170 °C	63	**8b**	2-Lithiofuran, THF, –78 °C[a]	**9c**	89
4				**8a**	2-Lithiofuran, THF, –78 °C[a]	**9d**	91
5	**7c**	$Si(OEt)_4$, 170 °C	94	**8c**	*n*-BuLi, THF, –78 °C	**9e**	51

[a] 2-Lithiofuran was generated in situ by the reaction of *n*-BuLi and furan.



Scheme 4

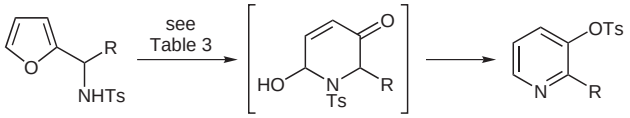
Table 2 Optimisation of the Aromatisation of the Pyridinone **10a** to the Pyridine **11a**

Entry	Lewis acid	Solvent	Temp (°C)	Quench	Yield (%), **11a**
1	$Yb(OTf)_3$	CH_2Cl_2	25	–	0[a]
2	$ZnCl_2$	CH_2Cl_2	25	–	<10[a]
3	BCl_3	CH_2Cl_2	25	–	<25[a]
4	$BF_3{\cdot}OEt_2$	CH_2Cl_2	25	Et_3N	38
5	$BF_3{\cdot}OEt_2$	CH_2Cl_2	25	MeOH	0[b]
6	$SnCl_4$	CH_2Cl_2	25	Et_3N	45
7	$AlCl_3$	CH_2Cl_2	25	Et_3N	47
8	$SnCl_4$	CH_2Cl_2	–78	Et_3N	73
9	$AlCl_3$	CH_2Cl_2	–78	Et_3N	92
10	$SnCl_4$	THF	–78	–	0[a]

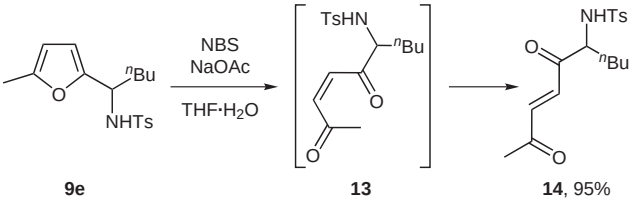
[a] Determined by analysis of the crude reaction mixture by analytical HPLC.
[b] The 3-hydroxypyridine **12** was isolated in 72% yield.

5). The 3-substituent of the pyridine could, therefore, be varied simply by changing the nature of the quench used.

With optimised conditions in hand, the scope and limitations of the cascade were investigated. Treatment of the sulfonamides **9b** and **9c** with MCPBA gave the pyridinones **10b** and **10c**; upon exposure to Lewis acid ($AlCl_3$, CH_2Cl_2, –78 °C), followed by treatment with triethylamine, the pyridines **11b** and **11c** were obtained (Scheme 5 and Table 3, entries 2 and 3). Oxidation of the difurylsulfonamide **9d** with NBS gave the pyridine **11d** directly; in this case, Lewis acid mediated aromatisation was not required (entry 4).[12] In contrast, treatment of the sulfonamide **9e** with either NBS or MCPBA gave the *trans*-enedione **14** (Scheme 6 and Table 3, entry 5). Presumably, initial oxidation produced the intermediate *cis*-enedione **13**, which underwent *cis*→*trans* isomerisation (Scheme 6). Similar olefin isomerisations have been reported upon exposure of *cis*-enediones to NBS.[16]



Scheme 5

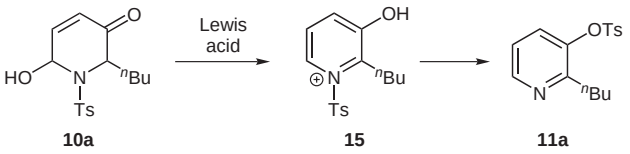


Scheme 6

We propose that aromatisation of the pyridinone **10a** occurred via acid-catalysed dehydration and enolisation to give the pyridinium salt **15** (Scheme 7). Presumably, intermolecular N→O *p*-toluenesulfonyl transfer then occurred to give the pyridine **11a**. With a methanol quench, we suggest that the intermediate **15** is intercepted to yield the 3-hydroxypyridine **12**. The pyridinium derivative **15** is analogous to the acylated DMAP complexes which are intermediates in many acylation reactions (Scheme 7).[17] A similar mechanism may account for the formation of the pyridines **11b–d**.

Table 3 Oxidation and Aromatisation of the α-Furylsulfonamides **10a–e**

Entry	Substrate	Conditions	Product	Yield (%)
1	**9a**	(1) NBS, NaOAc, THF–H_2O, 0 °C (2) $AlCl_3$, CH_2Cl_2, −78 °C (3) Et_3N	**11a**	92
2	**9b**	(1) MCPBA (2) $AlCl_3$, CH_2Cl_2, –78 °C (3) Et_3N	**11b**	81
3	**9c**	(1) MCPBA (2) $AlCl_3$, CH_2Cl_2, –78 °C (3) Et_3N	**11c**	36
4	**9d**	NBS, NaOAc, THF–H_2O, 0 °C	**11d**	50
5	**9e**	NBS, NaOAc, THF–H_2O, 0 °C	**14**	95



Scheme 7

In summary, an oxidative cascade has been developed and exploited in the synthesis of a range of 2-substituted-3-sulfonyloxypyridines from simple α-furyl sulfonamides. The method allowed the synthesis of pyridines with aryl, heteroaryl or alkyl 2-substituents. The reaction proceeded with N→O sulfonyl transfer, a process which could be prevented by quenching with methanol. However, it was not possible to prepare a 6-substituted pyridine because *cis→trans* isomerisation of the intermediate enedione competed with aromatisation. The method may find application in the synthesis of other 2,3-disubstituted pyridines.

Aromatisation of *N*-Sulfonyl Pyridinones

Compound 11a

To a stirred solution of the pyridinone **10a** (115 mg, 0.356 mmol) in CH_2Cl_2 (8 mL) was added $AlCl_3$ (427 μL of a 1 M solution in nitrobenzene, 0.427 mmol) at –78 °C. After 0.5 h, the reaction was quenched with Et_3N (0.5 mL) and was poured onto H_2O. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure to give a crude product. Purification by flash chromatography, eluting with 2:8 EtOAc–PE, gave the pyridine **11a** (100 mg, 92%) as a colourless oil, R_f 0.7 (4:6 EtOAc−PE). IR (film): ν_{max} = 1598, 1440, 1314, 1162, 1112 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.43 (1 H, dd, *J* = 4.7, 1.1 Hz, 6-H), 7.72 (2 H, d, *J* = 8.1 Hz, tosyl 3- and 5-H), 7.51 (1 H, dd, *J* = 8.3, 1.1 Hz, 4-H), 7.34 (2 H, d, *J* = 8.1 Hz, tosyl 2- and 6-H), 7.13 (1 H, dd, *J* = 8.3, 4.7 Hz, 5-H), 2.46 (3 H, s, tosyl Me), 1.48 (2 H, m, 1′-H), 1.26 (4 H, m, 2′- and 3′-H), 0.86 (3 H, m, 4′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.5, 147.9, 146.3, 145.1, 133.0, 130.4, 129.8, 128.8, 122.2, 32.2, 30.8, 23.0, 22., 14.2. MS (ES^+): *m/z* (%) = 306 (100) [MH^+]. HRMS: *m/z* calcd for $C_{16}H_{19}NO_3S$: [MH]: 306.1164. Found [MH^+]: 306.1163.

Compound 11b

R_f = 0.6 (4:6 EtOAc–PE). IR (film): ν_{max} = 2091, 1643, 1377, 1192, 1084 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.49 (1 H, dd, *J* = 4.6, 1.4 Hz, 6-H), 7.73 (2 H, d, *J* = 8.3 Hz, tosyl 3- and 5-H), 7.49 (1 H, dd, *J* = 8.2, 1.4 Hz, 4-H), 7.34 (2 H, d, *J* = 8.3 Hz, tosyl 2- and 6-H), 7.12 (1 H, dd, *J* = 8.2, 4.6 Hz, 5-H), 3.13 (1 H, sept, *J* = 6.8 Hz, 1′-H), 2.46 (3 H, s, tosyl-Me), 1.03 (6 H, d, *J* = 6.8 Hz, 2′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.8, 148.1, 146.3, 130.4, 128.9, 122.1, 29.1, 22.1, 21.8. MS (ES^+): *m/z* (%) = 292 (95) [MH^+]. HRMS: *m/z* calcd for $C_{15}H_{17}NO_3S$ [MH]: 292.1007. Found [MH^+]: 292.1000.

Compound 11c

R_f = 0.7 (4:6 EtOAc–PE). IR (film): ν_{max} = 1597, 1429, 1377, 1168, 1091 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.47 (1 H, dd, *J* = 3.9, 1.5 Hz, pyr 6-H), 7.74 (1 H, dd, *J* = 8.2, 1.5 Hz, pyr 4-H), 7.31 (2 H, d, *J* = 8.2 Hz, tosyl 3- and 5-H), 7.17 (4 H, m, 3′-, 4′- and 5′-H and pyr 5-H), 7.04 (2 H, dd, *J* = 8.2, 1.4 Hz, 2′- and 6′-H), 6.79 (2 H, d, *J* = 8.2 Hz, tosyl 2- and 6-H), 2.20 (3 H, s, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.7, 148.5, 145.7, 136.3, 132.9, 131.5, 129.8, 129.5, 129.1, 128.4, 128.2, 123.6, 115.0, 22.0. MS (ES^+): *m/z* (%) = 326 (100) [MH^+]. HRMS: *m/z* calcd for $C_{18}H_{15}NO_3S$ [MH]: 326.0851. Found [MH^+]: 326.0857.

Compound 11d[12]

R_f = 0.3 (3:7 EtOAc–PE). IR (film): ν_{max} = 1435, 1377, 1195, 1174, 1093 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 8.52 (1 H, dd, *J* = 4.6, 1.4 Hz, pyr 6-H), 7.71 (1 H, dd, *J* = 8.3, 1.4 Hz, pyr 4-H), 7.59 (2 H, d, *J* = 8.4 Hz, tosyl 3- and 5-H), 7.47 (1 H, dd, *J* = 1.7, 0.6 Hz, furyl 5-H), 7.19 (1 H, dd, *J* = 8.3, 4.6 Hz, pyr 5-H), 6.79 (2 H, d, *J* = 8.4 Hz, tosyl 2- and 6-H), 7.04 (1 H, dd, *J* = 3.4, 0.6 Hz, furyl 3-H), 6.45 (1 H, dd, *J* = 3.4, 1.7 Hz, furyl 4-H), 2.37 (3 H, s, Me). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 148.6, 147.7, 145.9, 143.8, 131.9, 130.7, 129.5, 128.5, 127.9, 126.4, 122.3, 111.8, 113.8, 21.6. MS (EI): *m/z* (%) = 315 (28 [M^+], 160 (61), 132 (100), 39 (62). HRMS: *m/z* calcd for $C_{16}H_{13}NO_4S$ [MH]: 316.0643. Found [MH^+]: 316.0642.

Compound 12

To a stirred solution of the pyridinone **10a** (50 mg, 0.148 mmol) in CH_2Cl_2 (7 mL) was added $BF_3{\cdot}OEt_2$ (21 μL, 0.163 mmol). After 0.1 h, MeOH (25 μL, 0.178 mmol) was added, the resulting solution was stirred for 0.1 h and concentrated under reduced pressure to give a crude product. Purification by flash chromatography, eluting with 40:60 EtOAc–PE, gave the pyridinol **12** (16 mg, 71%) as a colourless oil, R_f = 0.3 (40: 60 EtOAc–PE). IR (film): ν_{max} = 2958, 2930, 1577, 1457, 1288 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.99 (1 H, dd, *J* = 4.8, 2.2 Hz, 6-H), 7.18 (1 H, dd, *J* = 8.1, 2.2 Hz, 4-H),

7.04 (1 H, dd, *J* = 8.1, 4.8 Hz, 5-H), 2.90 (2 H, t, *J* = 7.7 Hz, 1′-H), 1.70 (2 H, p, *J* = 7.7 Hz, 2′-H), 1.38 (2 H, m, 3′-H), 0.90 (3 H, t, *J* = 7.5 Hz, 4′-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 151.8, 150.1, 138.4, 123.5, 122.5, 31.5, 30.6, 22.7, 13.9. MS (ES^+): *m/z* (%) = 152 (100) [MH^+].

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