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An efficient synthesis of furyl sulfonamides from the reaction of furan with in situ generated *N*-tosyl imines

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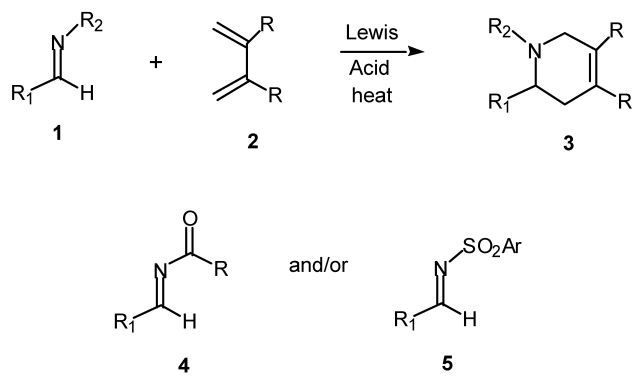
Abstract—Treatment of an aldehyde and furan with *N*-sulfinyl-*p*-toluenesulfonamide/zinc chloride leads to the formation of furyl sulfonamides via an in situ generated *N*-tosyl imine intermediate. In one case, a novel 4-tosylamino-5,6-dihydro-4*H*-3-oxa-benz[*e*]azulene was obtained by intramolecular aromatic substitution of the activated imine at the 3-position of the furan ring.

1. Introduction

The imino Diels–Alder reaction has become a highly useful tool for the construction of a variety of tetrahydropyridines.[1] Both inter- and intramolecular versions of this cycloaddition have been widely utilized in alkaloid synthesis.[2] Imines, however, are relatively unreactive dienophiles unless the cycloaddition is catalyzed by protonation of the imine[3] or when the imine is complexed by a Lewis acid.[4] A good alternative for simple imines in the [4+2]-cycloaddition is to utilize the more reactive acyl imine (**4**)[5] or sulfonyl imine (**5**).[6] Previous studies with these imines have demonstrated that a variety of dienes can be used for the imino-Diels–Alder reaction.[7,8] Our ongoing efforts dealing with the synthesis of biologically active alkaloids have been based, in part, on the use of substituted amido furans for intramolecular Diels–Alder cycloaddition chemistry.[9] Although furans[10] and isobenzofurans[11] are frequently employed as 4π-substrates, little is known about the imino Diels–Alder reaction of furans with activated imines. As a consequence of our ongoing efforts in this area, we thought it might be possible to access a variety of alkaloid natural products by employing an imino Diels–Alder cycloaddition of furans with activated imines (i.e. Scheme 2).

2. Results and discussion

A number of years ago both Kresze[12] and Weinreb[13] showed that non-enolizable aldehydes could be converted to the corresponding *N*-tosyl imines (i.e. **6**) using *N*-sulfinyl-*p*-toluenesulfonamide in the presence of a Lewis acid and that the in situ formed *N*-sulfonyl imines could be efficiently trapped with several dienes in a [4+2]-cycloaddition reaction (Scheme 1).[7] As part of our cycloaddition program, we envisioned using the Kresze/Weinreb protocol to generate various activated imines in the presence of furan with the hope of inducing a Diels–Alder reaction across the furan ring so as to ultimately generate 1,6-dihydro-2*H*-pyridin-3-ones (**8**) via the rearrangement of the transient [4+2]-cycloadduct **7** (Scheme 2). A trial reaction of imine **6** (R=*i*Pr), generated by treating isobutyraldehyde with *N*-sulfinyl-*p*-toluenesulfonamide[14] and zinc chloride in THF, with furan gave no signs of any product derived from a [4+2]-cycloaddition. However, the reaction proved to be extremely efficient and gave rise to a single product in 83% isolated yield whose structure was established as furanyl *p*-toluenesulfonamide **9** as evidenced from its spectral properties (Scheme 3). The structure of **9** was unequivocally established by an X-ray crystallographic study. Presumably, the formation of **9** occurs by initial activation of tosyl imine **6** with zinc chloride followed by



Scheme 1.

Keywords: *N*-tosyl imine; furyl sulfonamide; dihydro-4*H*-3-oxa-benz[*e*]azulene; furan; heteroaromatic; substitution.

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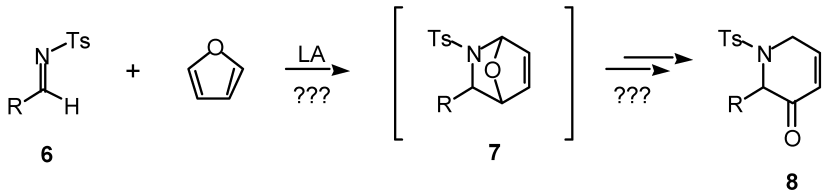
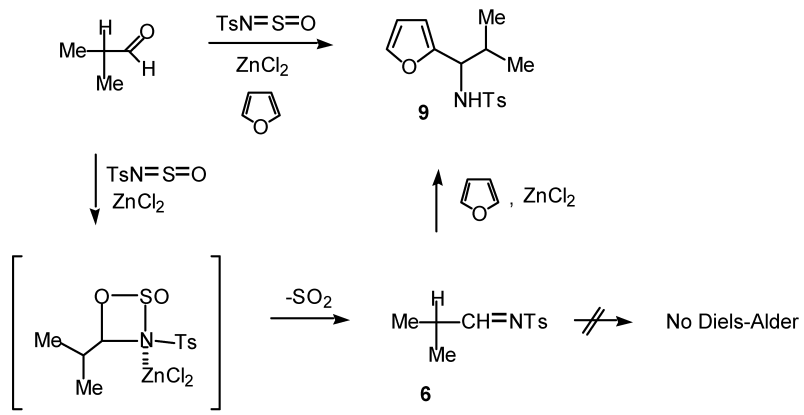


Scheme 2.



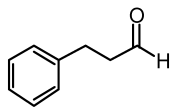
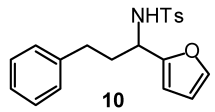
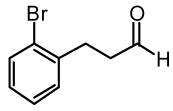
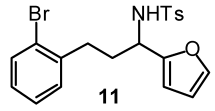
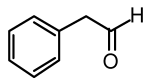
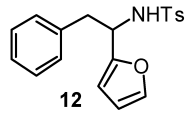
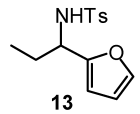
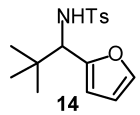
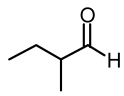
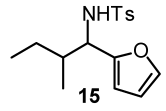
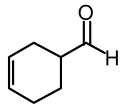
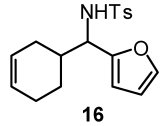
Scheme 3.

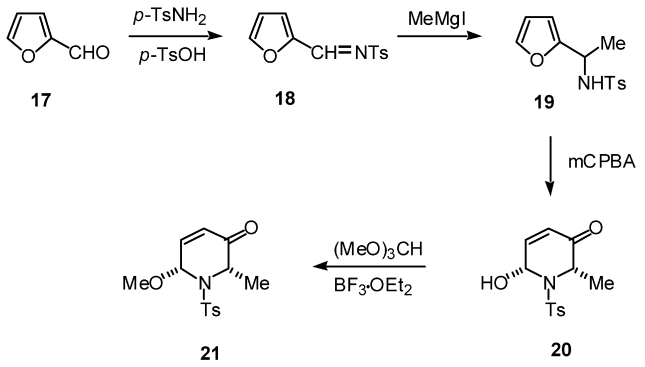
electrophilic aromatic substitution on the heteroaromatic framework of furan.[15] The reaction proved to be quite general and proceeded smoothly with a variety of aldehydes to furnish *p*-toluenesulfonamides **10**-**16** in ca. 80% yield (Table 1). Previous work by Ciufolini and Wood[16] provides good precedence for the observed reaction since these workers demonstrated that the reaction of α-hydroxy amides with furan afforded *N*-acyl 2-furylamines in good yield. Similarly, imino acetates have been found to react with furan under thermal conditions to furnish furfuryl amines.[17]

It was also possible to synthesize a related furyl sulfonamide (e.g. **19**) by condensation of furfural (**17**) with *p*-toluenesulfonamide using *p*-TsOH as the Lewis acid (Scheme 4). Treatment of the resulting imine **18** with methyl magnesium iodide produced **19** in 95% yield. Furyl sulfonamides such as **10**-**16** (and **19**) are useful substrates for alkaloid synthesis as they readily undergo the aza-Achmatowicz reaction, a process defined as the conversion of furyl amides into 1,6-dihydro-2*H*-pyridin-3-ones.[18] This novel rearrangement has been used for the synthesis of azasaccharides,[19] izidine structures, β-lactam intermediates, trisubstituted piperidines[20] and unusual amino acids. In fact, 6-methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (**21**) could be prepared from furyl sulfonamide **19** in 2 steps in 72% overall yield (Scheme 4). The stereochemical assignment of **21** as the *cis*-isomer is based on NMR spectroscopic analysis (1D NOE). The exclusive formation of **21** can be rationalized by assuming the $A^{1,3}$-strain between the two substituents and the tosyl group forces the methoxy and methyl groups to adopt a pseudoaxial orientation.

In an attempt to enhance the desired [4+2]-cycloaddition of a tosyl imine across the furan ring, we attempted to carry out

Table 1.

Entry	Aldehyde	Product	Yield (%)
a		 **10**	81
b		 **11**	77
c		 **12**	80
d		 **13**	73
e		 **14**	82
f		 **15**	81
g		 **16**	81



Scheme 4.

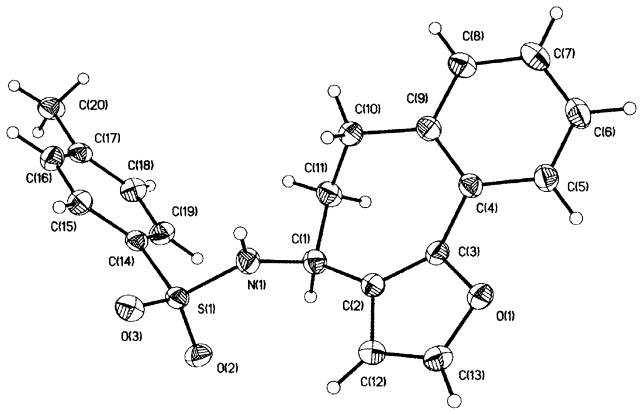
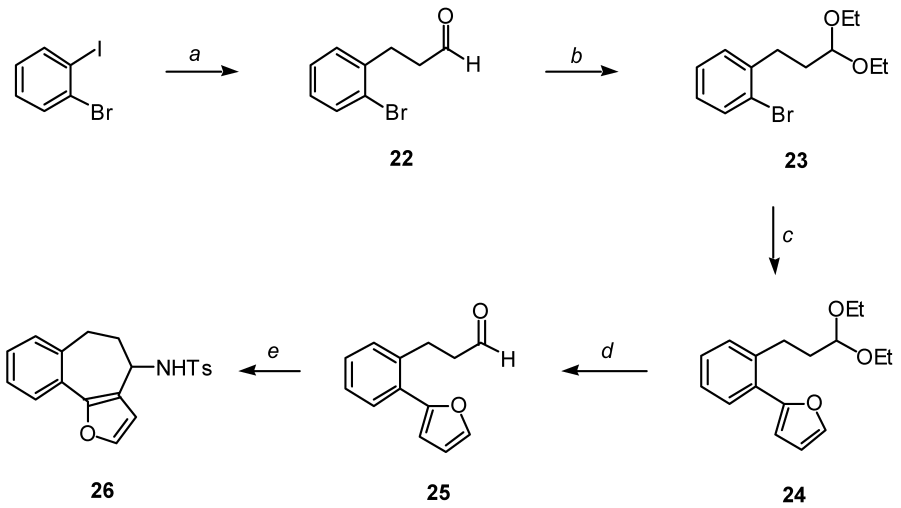


Figure 1. Ortep drawing of *N*-(5,6-dihydro-4*H*-3-oxa-benzo[*e*]azulen-4-yl)-4-methyl-benzenesulfonamide (**26**).



Scheme 5. *Reagents*: (a) $CH_2{=}CHCH_2OH$, DMF, $C_6H_5CH_2N(C_2H_5)_3Cl$, $NaHCO_3$, $Pd(OAc)_2$, 83%; (b) $(EtO)_3CH$, NBS, EtOH, 92%; (c) 2-furanylB$(OH)_2$, $Pd(PPh_3)_4$, benzene, Na_2CO_3, 89%; (d) thiourea, EtOH, H_2O, 50%; (e) TsNSO, $ZnCl_2$, CH_2Cl_2, 97%.

an intramolecular Diels–Alder reaction (IMDAF).[21] Not only do IMDAF reactions allow for the preparation of complex oxygenated polycyclic compounds, but they often proceed at lower temperatures than their intermolecular counterparts. With this in mind, we investigated the $ZnCl_2$-induced reaction of aldehyde **25** with *N*-sulfinyl-*p*-toluenesulfonamide with the hope of obtaining an IMDAF product. Synthesis of the required aldehyde **25** was carried out in 5 steps from commercially available starting materials (Scheme 5). Thus, treatment of 2-bromo-iodobenzene with allyl alcohol, benzyltriethylammonium chloride and palladium(II) acetate afforded 3-(2-bromophenylpropional-dehyde (**22**) in 83% yield.[22] Protection of **22** as the diethoxy acetal **23** proceeded uneventfully in 92% yield. Coupling of the furan segment to the aromatic ring was accomplished using 2-furanboronic acid and palladium tetrakis(triphenyl-phosphine) which afforded 3-(2-furan-2-ylphenyl)propion-aldehyde (**25**) after hydrolysis of acetal **24**. The reaction of **25** with *N*-sulfinyl-*p*-toluenesulfonamide and zinc chloride delivered a single product in 97% yield which was assigned as the unusual fused furan **26** based upon its spectroscopic properties. This structure was unequi-vocally established by an X-ray crystallographic study (see Fig. 1).

In conclusion, our attempts to carry out an imino Diels–Alder reaction between a tosyl imine and a furan remain elusive. We have, however, developed an efficient synthesis of furyl sulfonamides from the reaction of aldehydes with *N*-sulfinyl-*p*-toluenesulfonamide and furan. The synthesis proved to be quite general with respect to the starting aldehyde used. In one case, a novel 4-tosylamino-5,6-dihydro-4*H*-3-oxabenz[*e*]azulene was obtained by intra-molecular aromatic substitution of the activated imine at the 3-position of the furan ring. The scope and generality of this cyclization will be the subject of future investigations.

3. Experimental

3.1. General

Melting points are uncorrected. Mass spectra were deter-mined at an ionizing voltage of 70 eV. Unless otherwise noted, all reactions were performed in flame dried glassware under an atmosphere of dry argon. Solutions were evaporated under reduced pressure with a rotary evaporator and the residue was chromatographed on a silica gel column using an ethyl acetate/hexane mixture as the eluent unless

specified otherwise. All solids were recrystallized from ethyl acetate/hexane for analytical data.

3.1.1. *N*-(1-Furan-2-yl-2-methyl-propyl)-4-methyl-benzenesulfonamide (9). To a solution containing 1.9 g (9 mmol) of *N*-sulfinyl-*p*-toluenesulfonamide in 12 mL of THF was added 0.6 mL (6 mmol) of isobutyraldehyde, 0.9 mL (12 mmol) of furan and 12 mL of $ZnCl_2$ in THF (0.5 M) at 0°C. After stirring at 0°C for 2 h and at 25°C for 16 h, 24 mL of CH_2Cl_2 was added to the reaction mixture. The solution was subjected to flash silica gel chromatography in order to remove the $ZnCl_2$. The eluent was concentrated under reduced pressure and the residue was purified by flash silica gel chromatography to give **9** as a white solid: mp 119–120°C; IR (KBr) 3266, 1437, 1322, and 1164 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.78 (d, J=6.6 Hz, 3H), 0.93 (d, J=6.6 Hz, 3H), 2.02 (dd, J=6.9, 6.6 Hz, 1H), 2.39 (s, 3H), 4.13 (dd, J=9.6, 7.2 Hz, 1H), 5.36 (d, J=9.3 Hz, 1H), 5.79 (d, J=3.0 Hz, 1H), 6.03 (dd, J=3.0, 1.8 Hz, 1H), 7.09–7.12 (m, 1H), 7.13 (d, J=7.8 Hz, 2H), and 7.58 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.0, 19.1, 21.7, 33.2, 57.9, 107.5, 110.1, 127.2, 129.5, 137.9, 141.7, 143.1, and 152.7. Anal. calcd for $C_{15}H_{18}NO_3S$: C, 61.41; H, 6.53; N, 4.77. Found: C, 61.42; H, 6.51; N, 4.73.

3.1.2. *N*-(1-Furan-2-yl-3-phenylpropyl)-4-methyl-benzenesulfonamide (10). The title compound was prepared in 81% yield; mp 93–94°C; IR (KBr) 3303, 1454, 1314, and 1156 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.10 (dd, J=7.8, 7.5 Hz, 2H), 2.38 (s, 3H), 2.54–2.61 (m, 2H), 4.43 (dd, J=8.4, 7.2 Hz, 1H), 5.42 (d, J=8.7 Hz, 1H), 5.93 (d, J=3.0 Hz, 1H), 6.12 (dd, J=3.0, 1.8 Hz, 1H), 7.09 (d, J=6.9 Hz, 2H), 7.14–7.28 (m, 4H), 7.17 (d, J=8.1 Hz, 2H), and 7.63 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.7, 32.1, 36.7, 51.5, 107.3, 110.2, 126.3, 127.2, 128.7, 129.6, 137.9, 141.1, 142.1, 143.3, 153.0. Anal. calcd for $C_{15}H_{18}NO_3S$: C, 67.58; H, 5.95; N, 3.94. Found: C, 67.49; H, 6.02; N, 4.04.

3.1.3. *N*-[3-(2-Bromophenyl)-1-furan-2-yl-propyl]-4-methyl-benzenesulfonamide (11). The title compound was prepared in 77% yield; mp 78–79°C; IR (KBr) 3250, 1470, 1320, and 1160 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.07 (dd, J=7.2, 1.8 Hz, 2H), 2.37 (s, 3H), 2.58–2.80 (m, 2H), 4.46 (dt, J=9.0, 6.9 Hz, 1H), 5.27 (d, J=9.0 Hz, 1H), 5.97 (d, J=3.0 Hz, 1H), 6.12 (dd, J=3.3, 1.8 Hz, 1H), 7.04 (dt, J=7.8, 2.1 Hz, 1H), 7.14–7.19 (m, 3H), 7.18 (d, J=8.1 Hz, 2H), 7.48 (dd, J=7.8, 0.9 Hz, 1H), and 7.63 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.8, 32.7, 35.1, 51.6, 107.4, 110.3, 124.6, 127.3, 127.8, 128.2, 129.7, 130.8, 133.1, 137.9, 140.5, 142.2, 143.4, and 152.9. Anal. calcd for $C_{20}H_{20}BrNO_3S$: C, 55.30; H, 4.64; N, 3.22. Found: C, 55.09; H, 4.56; N, 3.08.

3.1.4. *N*-(1-Furan-2-yl-2-phenylethyl)-4-methyl-benzenesulfonamide (12). The title compound was prepared in 80% yield; mp 110–111°C; IR (KBr) 3261, 1423, 1320, and 1155 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3H), 3.08 (dd, J=7.2, 3.0 Hz, 1H), 4.66 (dt, J=7.8, 7.2 Hz, 1H), 5.14 (d, J=8.1 Hz, 1H), 5.86 (d, J=3.6 Hz, 1H), 6.11 (dd, J=3.3, 1.8 Hz, 1H), 6.92 (dd, J=5.7, 2.4 Hz, 1H), 7.14–7.19 (m, 3H), 7.15 (d, J=5.7 Hz, 2H), 7.17–7.21 (m, 5H), and 7.57 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.8, 41.3, 53.2, 107.9, 110.4, 127.1, 127.2, 128.7, 129.6, 129.7, 136.4, 137.7, 142.1, 143.3, and 152.5. Anal. calcd for $C_{19}H_{19}NO_3S$: C, 66.84; H, 5.61; N, 4.10. Found: C, 66.74; H, 5.63; N, 4.07.

3.1.5. *N*-(1-Furan-2-yl-2-propyl)-4-methyl-benzenesulfonamide (13). The title compound was prepared in 73% yield; mp 92–93°C; IR (KBr) 3257, 1425, 1322, and 1161 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.81 (t, J=7.2 Hz, 3H), 1.79 (dt, J=7.5, 7.2 Hz, 2H), 2.36 (s, 3H), 4.31 (dd, J=8.1, 7.5 Hz, 1H), 5.23 (d, J=8.7 Hz, 1H), 5.90 (d, J=3.3 Hz, 1H), 6.09 (dd, J=3.3, 2.1 Hz, 1H), 7.11–7.12 (m, 1H), 7.17 (d, J=8.1 Hz, 2H), and 7.62 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 10.3, 21.6, 28.2, 53.3, 107.0, 110.0, 127.1, 129.5, 137.9, 141.9, 143.1, and 153.1. Anal. calcd for $C_{14}H_{17}NO_3S$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.17; H, 6.11; N, 4.95.

3.1.6. *N*-(1-Furan-2-yl-2,2-dimethyl-propyl)-4-methyl-benzenesulfonamide (14). The title compound was prepared in 42% yield; mp 179–181°C; IR (KBr) 3260, 1433, 1324, and 1163 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.91 (s, 9H), 2.31 (s, 3H), 4.04 (d, J=10.2 Hz, 1H), 5.49 (d, J=10.2 Hz, 1H), 5.72 (d, J=3.3 Hz, 1H), 5.98 (dd, J=3.0, 1.2 Hz, 1H), 7.05 (d, J=1.2 Hz, 1H), 7.07 (d, J=8.1 Hz, 2H), and 7.51 (d, J=8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.7, 26.8, 35.8, 61.0, 108.1, 110.0, 127.1, 129.4, 137.5, 141.4, 143.0, and 152.1. Anal. calcd for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89; N, 4.56. Found: C, 62.45; H, 6.85; N, 4.65.

3.1.7. *N*-(1-Furan-2-yl-2-methyl-butyl)-4-methyl-benzenesulfonamide (15). The title compound was prepared in 81% yield; mp 75–76°C; IR (KBr) 3270, 1436, 1324, and 1162 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.73–0.92 (m, 6H), 1.01–1.14 (m, 1H), 1.29–1.54 (m, 1H), 1.75–1.81 (m, 1H), 2.34 (s, 3H), 4.19–4.29 (m, 1H), 5.29 (t, J=9.6 Hz, 1H), 5.78 (d, J=3.3 Hz, 1H), 6.03–6.05 (m, 1H), 7.09 (d, J=1.5 Hz, 1H), 7.13 (dd, J=8.4, 1.5 Hz, 2H), and 7.57 (dd, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.4, 11.6, 15.3, 15.5, 21.7, 25.7, 26.0, 39.7, 56.4, 76.9, 107.3, 107.6, 110.0, 110.1, 127.1, 129.5, 137.9, 141.7, 143.1, 152.5, and 153.0. Anal. calcd for $C_{16}H_{21}NO_3S$: C, 62.51; H, 6.89; N, 4.56. Found: C, 62.32; H, 6.79; N, 4.74.

3.1.8. *N*-(1-Cyclohex-3-enyl-1-furan-2-yl-methyl)-4-methyl-benzenesulfonamide (16). The title compound was prepared in 81% yield; mp 86–88°C; IR (KBr) 3281, 1437, 1331, and 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.13–1.48 (m, 1H), 1.69–2.22 (m, 6H), 2.34 (s, 3H), 4.17–4.24 (m, 1H), 5.41 (dt, J=7.2, 2.7 Hz, 1H), 5.52 (d, J=9.6 Hz, 1H), 5.61 (s, 1H), 5.78 (dd, J=10.8, 3.3 Hz, 2H), 6.01–6.04 (m, 1H), 7.09 (dd, J=1.8, 0.6 Hz, 1H), 7.12 (dd, J=8.1, 1.5 Hz, 2H), and 7.56 (dd, J=8.1, 2.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.7, 25.0, 25.2, 25.4, 28.4, 28.5, 38.4, 38.5, 56.1, 56.4, 107.7, 107.8, 110.0, 125.6, 125.9, 127.0, 127.1, 127.3, 130.0, 137.9, 141.9, 143.1, and 152.3. Anal. calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23. Found: C, 65.08; H, 6.41; N, 4.32.

3.1.9. *N*-(1-Furan-2-yl-ethyl)-4-methyl-benzenesulfonamide (19). A 28.1 g (292 mmol) sample of furfural (**17**),

300 mL of toluene, *p*-toluenesulfonamide (40 g, 234 mmol) and *p*-toluenesulfonic acid (0.5 g, 2.9 mmol) were placed in a round bottom flask with a Dean Stark trap and heated at reflux for 10 h. The reaction turned a deep brown color. After 10 h, charcoal was added to the hot solution and the mixture was stirred for 1 h and filtered. The solvent was removed under reduced pressure to give *N*-furan-2-ylmethylene-4-methyl-benzenesulfonamide (**18**) as a brown solid. Recrystallization from benzene gave pure brown crystals of **18** in 85% yield (62 g, 248 mmol); mp 100–101°C; IR (thin film) 1605, 1542, 1467, 1319, 1289, 1089, and 1023 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 6.63 (dd, 1H, J=2.8, 1.6 Hz), 7.33 (m, 3H), 7.73 (d, 1H, J=1.6 Hz), 7.86 (dd, 2H, J=6.8, 2.8 Hz) and 8.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 113.7, 124.7, 128.0, 128.2, 129.7, 135.1, 144.5, 149.7, and 155.6.

The above compound (1.0 g, 4.0 mmol) was dissolved in 15 mL of THF and cooled to 0°C and methyl magnesium bromide (2.7 mL of a 3.0 M solution (8.0 mmol)) was added to the solution. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution (30 mL) and 30 mL of ether was added. The solution was extracted with ether, the layers were separated, and the organic layer was dried ($MgSO_4$). Concentration under reduced pressure and purification by silica gel chromatography gave 1.0 g (3.8 mmol, 95%) of *N*-(1-furan-2-yl-ethyl)-4-methyl-benzenesulfonamide (**19**): mp 72–73°C (lit.[23] mp 72–72.3°C); IR (thin film) 1599, 1427, 1333, 1152, and 1093 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (d, 3H, J=7.2 Hz), 2.37 (s, 3H), 4.52 (ddd, 1H, J=14.8, 7.2, 7.2 Hz), 5.37 (d, 1H, J=8.4 Hz), 5.97 (dd, 1H, J=3.2, 0.8 Hz), 6.12 (dd, 1H, J=3.2, 1.6 Hz), 7.14 (dd, 1H, J=1.6, 0.8 Hz), 7.21 (d, 2H, J=8.4 Hz), and 7.68 (d, 2H, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7, 21.4, 47.2, 106.0, 109.9, 126.9, 129.3, 137.5, 143.0, 141.7, and 154.0.

3.1.10. 6-Methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (21). A 0.39 g (1.1 mmol) sample of sulfonamide **19**, 4 mL of CH_2Cl_2, and *m*-CPBA (0.39 g, 2.3 mmol) were placed in a round bottom flask and the mixture was stirred for 2 h. The reaction was quenched with a saturated aqueous $NaHCO_3$ solution (15 mL) and 15 mL of ether was added. The solution was extracted with ether, the layers were separated, and the organic layer was dried ($MgSO_4$). Concentration under reduced pressure and purification by silica gel chromatography gave 0.27 g (0.96 mmol, 85%) of 6-hydroxy-2-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (**20**); IR (thin film) 1686, 1597, 1449, 1332, 1165, 1110, and 1006 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.59 (d, J=7.2 Hz, 3H), 2.38 (s, 3H), 3.82 (bs, 1H), 4.36 (q, 1H, J=7.2 Hz), 5.90 (dd, 1H, J=4.8, 1.2 Hz), 5.96 (dd, 1H, J=10.0, 1.2 Hz), 6.86 (dd, 1H, J=10.4, 4.8 Hz), 7.25 (d, 2H, J=8.4 Hz), and 7.62 (d, 2H, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 22.1, 57.0, 73.3, 126.2, 126.7, 130.0, 136.5, 143.5, 144.3, and 195.3.

A 1.0 g (3.5 mmol) sample of 6-hydroxy-2*H*-pyridin-3-one (**20**) was dissolved in 20 mL of CH_2Cl_2 and trimethyl orthoformate (777 μL, 7.1 mmol) and $BF_3{\cdot}OEt_2$ (45 μL, 0.36 mmol) were added to the solution. The solution was stirred for 3 h at 0°C and was quenched with a saturated aqueous $NaHCO_3$ solution (25 mL) and 40 mL of ether was added. The solution was extracted with ether, the layers were separated, and the organic layer was dried ($MgSO_4$). Concentration under reduced pressure and purification by silica gel chromatography gave 0.89 g (3.0 mmol, 85%) of 6-methoxy-2-methyl-1-(toluene-4-sulfonyl)-1,6-dihydro-2*H*-pyridin-3-one (**21**); mp 113–115°C; IR (thin film) 1692, 1597, 1453, 1340, 1168, 1080, and 1014 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.56 (d, 3H, J=7.6 Hz), 2.38 (s, 3H), 3.57 (s, 3H), 4.30 (q, 1H, J=7.6 Hz), 5.58 (dd, 1H, J=4.8, 0.8 Hz), 5.82 (dd, 1H, J=10.4, 0.8 Hz), 6.82 (dd, 1H, J=10.4, 4.8 Hz), 7.24 (dd, 2H, J=8.0, 1.2 Hz), and 7.56 (dd, 2H, J=8.0, 1.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 21.5, 56.0, 57.2, 80.7, 126.6, 126.8, 130.0, 136.1, 142.5, 144.1, and 195.5. Anal. calcd for $C_{14}H_{17}NO_4S$: C, 56.93; H, 5.81; N, 4.75. Found: C, 56.81; H, 5.69; N, 4.70.

3.1.11. 3-(2-Bromophenyl)propionaldehyde (22). A solution containing 14.2 g (50 mmol) of 2-bromo-iodobenzene, 8.7 g (150 mmol) of allyl alcohol, 10.5 g (125 mmol) of sodium hydrogencarbonate, 11.4 g (50 mmol) of benzyltriethylammonium chloride and 0.24 g (1 mmol) of palladium (II) acetate in 50 mL of DMF was stirred at 45°C for 20 h. The reaction mixture was cooled to room temperature and the precipitate was removed by filtration, followed by addition of 250 mL of CH_2Cl_2 and 100 mL of water. The layers were separated and the aqueous layer was extracted with 100 mL of CH_2Cl_2. The combined organic layers were washed several times with water and brine, and concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to afford 8.8 g (83%) of **22** as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 2.80 (dt, J=7.5, 1.2 Hz, 2H), 3.07 (t, J=7.5 Hz, 2H), 7.06–7.12 (m, 1H), 7.24–7.27 (m, 2H), 7.55 (d, J=7.5 Hz, 1H), and 9.84 (t, J=1.2 Hz, 1H).

3.1.12. 1-Bromo-2-(3,3-diethoxypropyl)benzene (23). A solution containing 6.4 g (30 mmol) of aldehyde **22**, 10.0 mL of triethyl orthoformate (60 mmol) and 0.11 g of *N*-bromosuccinimide (0.6 mmol) in 90 mL of ethanol was stirred at room temperature for 1 h. After removal of the solvent under reduced pressure, 100 mL of ether and 50 mL of 10% of NaOH in water were added to the residue. The layers were separated and the aqueous layer was extracted with 50 mL of ether. The combined organic layers were washed with 50 mL of brine. After removal of the solvent under reduced pressure, the residue was subjected to flash silica gel chromatography to give 7.9 g (92%) of **23** as a yellow oil: IR (neat) 2974, 2877, 1471, and 1128 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.23 (t, J=7.2 Hz, 6H), 1.92–1.99 (m, 2H), 2.79–2.84 (m, 2H), 3.45–3.58 (m, 2H), 3.61–3.73 (m, 2H), 4.54 (t, J=5.4 Hz, 1H), 7.03–7.08 (m, 1H), 7.22–7.24 (m, 2H), and 7.53 (d, J=7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6, 31.7, 33.7, 61.3, 66.1, 102.4, 124.7, 127.7, 127.9, 130.7, 133.1, and 141.3; MS (EI) m/z 286 $(M)^+$, 241, 197, 195, 171, 169, 103.

3.1.13. 2-[2-(3,3-Diethoxypropyl)phenyl]furan (24). To a solution containing 7.2 g (25 mmol) of acetal **23**, 3.4 g (26 mmol) of 2-furanboronic acid and 0.6 g (0.25 mmol) of tetrakis(triphenylphosphine) palladium (0) was added

dropwise 32 mL (125 mmol, 2 M) of sodium carbonate in water. The reaction mixture was heated to 100°C for 2 h and then cooled to room temperature. The precipitate was removed by filtration and the product was extracted with ether and washed with water. The aqueous layer was extracted several times with ether. The combined organic layers were washed several times with 10% of brine and saturated brine and then concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 6.1 g (89%) of **24** as a yellow oil: IR (neat) 2974, 2879, 1484, and 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22 (t, J=7.2 Hz, 6H), 1.89–1.97 (m, 2H), 2.89–2.95 (m, 2H), 3.44–3.54 (m, 2H), 3.61–3.66 (m, 2H), 4.53 (t, J=5.7 Hz, 1H), 6.49 (dd, J=3.3, 2.1 Hz, 1H), 6.61 (d, J=3.3 Hz, 1H), 7.23–7.30 (m, 3H), 7.50 (d, J=1.2 Hz, 1H), and 7.62 (dd, J=3.3, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6, 29.6, 34.9, 61.4, 102.9, 108.5, 111.6, 126.4, 128.1, 128.5, 128.6, 130.3, 130.5, 139.2, 142.1, and 153.9; MS (EI) m/z 274 $(M)^+$, 229, 207, 183, 157, 128, 103.

3.1.14. 3-(2-Furan-2-yl-phenyl)propionaldehyde (25). A solution of 5.5 g (20 mmol) of acetal **24** and 9.1 g (120 mmol) of thiourea in a mixture of 70 mL of ethanol and 70 mL of water was heated at reflux for 10 h. The solvent was removed under reduced pressure and the product was extracted with ether and washed with water. The aqueous layer was extracted several times with ether. The combined organic layers was washed with water, 10% of brine and then concentrated under reduced pressure. The residue was subjected to flash silica gel chromatography to give 2.1 g (50%) of **25** as a yellow oil: IR (neat) 1721 and 1484 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.75 (dt, J=7.2, 0.9 Hz, 2H), 3.17 (t, J=7.5 Hz, 2H), 6.49–6.53 (m, 2H), 7.26–7.29 (m, 3H), 7.51 (d, J=0.9 Hz, 1H), and 7.56–7.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.1, 45.1, 108.5, 111.7, 126.9, 128.5, 128.8, 130.3, 130.5, 137.8, 142.4, 154.0, and 202.0; MS (EI) m/z 200 $(M)^+$, 181, 172, 143, 129, 128, 115.

3.1.15. *N*-(5,6-Dihydro-4*H*-3-oxa-benzo[*e*]azulen-4-yl)-4-methyl-benzenesulfonamide (26). To a solution containing 0.4 g (2.0 mmol) of aldehyde **25** and 0.7 g (3.0 mmol) of *N*-sulfinyl-*p*-toluenesulfonamide in 17 mL of CH_2Cl_2 was added 4 mL of a 0.5 M (2.0 mmol) solution of $ZnCl_2$ in THF at 0°C. After stirring at 0°C for 2 h, and then at 25°C for 17 h, the solution was subjected to flash silica gel chromatography to remove the $ZnCl_2$. The eluent was concentrated under reduced pressure while maintaining the temperature at 20°C. The residue was purified by flash silica gel chromatography to give 0.69 g (97%) of **26** as a white solid: mp: 150–152°C; IR (KBr) 3273, 2940, 1492, 1444, 1324, and 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.87–1.94 (m, 1H), 2.11–2.19 (m, 1H), 2.48 (s, 3H), 2.79 (t, J=4.5 Hz, 2H), 4.52–4.58 (m, 1H), 4.75 (d, J=7.8 Hz, 1H), 5.91 (d, J=1.5 Hz, 1H), 7.14–7.29 (m, 2H), 7.32 (d, J=2.1 Hz, 2H), 7.37 (d, J=8.1 Hz, 2H), 7.81 (d, J=7.8 Hz, 1H), and 7.85 (d, J=8.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.8, 30.4, 32.5, 50.8, 113.0, 121.6, 125.7, 126.7, 127.3, 127.7, 129.2, 129.6, 130.1, 138.3, 139.0, 142.1, 143.8, and 149.1. Anal. calcd for $C_{20}H_{19}NO_3S$: C, 67.97; H, 5.42; N, 3.96. Found: C, 68.05; H, 5.46; N, 3.90; MS (FAB) m/z 308 $(M-H)^-$, 305, 280.

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