Preparation and Intramolecular Radical Cyclization of Some Cyclic *N*-Sulfonylenamines

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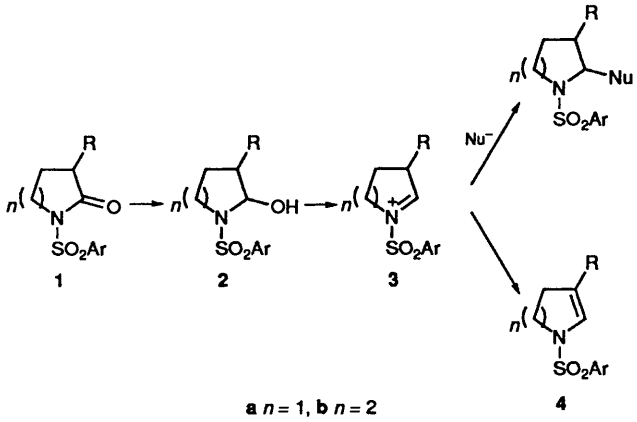
Cyclic *N*-sulfonylenamines can be prepared under mild conditions from the corresponding lactams by an efficient two-step procedure involving diisobutylaluminium hydride (DIBAL) or $LiAlH_4$ reduction followed by CF_3CO_2H induced dehydration. In addition, appropriately substituted *N*-sulfonylenamines are substrates in intramolecular radical cyclizations, forming the corresponding spirocyclic sulfonamides in good yields.

The importance of enamines as reactive intermediates in organic synthesis has increased steadily since the pioneering work by Stork and co-workers.[1] Thus, the conversion of an aldehyde or a ketone into a *C*-alkylated, acylated, carbocyclic or heterocyclic derivative by reaction of an appropriate electrophile with the corresponding enamine has become a part of the standard arsenal of efficient reactions.[2] In addition, enamides, *i.e.* *N*-formyl-, *N*-acyl- and *N*-(alkoxycarbonyl)-enamines, have been thoroughly investigated and also used as key intermediates in natural product synthesis.[3] Remarkably, in spite of the large effort expended in this area, there has been no thorough investigation on the preparation and reactivity of *N*-sulfonylenamines.[4] In an ongoing study we recently demonstrated that cyclic *N*-sulfonyliminium ions **3** (R = H), generated from α-hydroxy *N*-sulfonylamines **2** (R = H) under acidic conditions, react with a variety of carbon nucleophiles and thus offer a convenient entry to 2-substituted piperidines and pyrrolidines[5] (Scheme 1). It was also shown that when

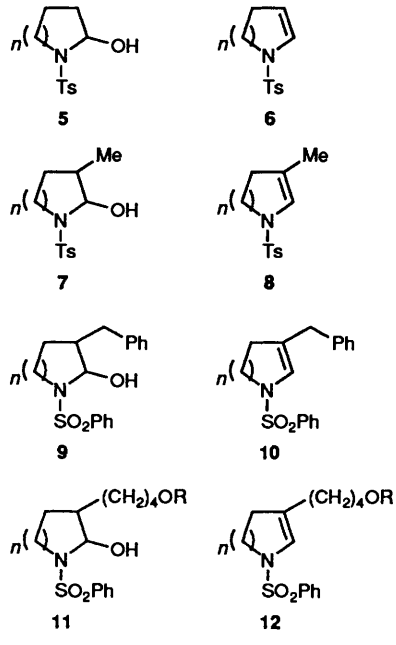


Scheme 1

using PPTS (pyridinium toluene-*p*-sulfonate) as a reaction promoter only the corresponding *N*-sulfonylenamines **4** (R = H) were formed and none of the expected product. Consequently, we became interested in optimizing this transformation and to investigate the feasibility of using amino alcohols **2** as precursors to the corresponding *N*-sulfonylenamines **4**. Herein we detail the results from this study and also describe the use of β-substituted *N*-sulfonylenamines in intramolecular radical spirocyclization reactions as a potential entry to biologically significant alkaloids.

Results and Discussion

Reduction of *N*-sulfonyllactams **1a**, **b** (R = H) with diisobutylaluminium hydride (DIBAL) or $LiAlH_4$ affords the corresponding α-hydroxy *N*-sulfonylamines **5a**, **b** in high yield, as discussed previously.[5] It was also shown that α-hydroxy *N*-sulfonylamines **5a**, **b** (R = H), when treated with allyltrimethylsilane and PPTS in dichloromethane (−78 °C ⟶ room temp.), afforded enamines **6a**, **b** (50–60%), respectively. Attempts to optimize this transformation by excluding the silane from the reaction mixture were somewhat puzzling, yielding only minor amounts of the enamine products along with recovered starting material. It seems reasonable to assume that the role of the silane in this reaction is to function as a water scavenger, thus promoting the formation of *N*-sulfonylenamines **6a**, **b**. In order to test this hypothesis and to investigate if other, more common, dehydrating agents could promote enamine formation, compounds **5a**, **b** were treated with molecular sieves (4 Å, 25% w/w) and PPTS under otherwise identical reaction conditions. Somewhat to our surprise this resulted in a complicated mixture of products from which the desired enamines could be isolated, at best, in a modest yield (40–50%). With these results in hand it was apparent that a more thorough screening of various Lewis and Brønstedt acids and their effect on the outcome of the reaction was required.



a *n* = 1, **b** *n* = 2, R = $SiBu^tPh_2$, Ts = *p*-$MeC_6H_4SO_2$

Initial attempts to dehydrate **5a**, **b** with various Lewis acids, *e.g.* $TiCl_4$, $Ti(OPr^i)_4$, $SnCl_4$, $FeCl_3$ or $BF_3{\cdot}OEt_2$, were un-

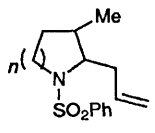
Table 1 Yields (%) of *N*-sulfonylenamines from α-hydroxy *N*-sulfonylamines[a]

Entry	Substrate	Product	Yield (%)
1	**5a**	**6a**	74
2	**5b**	**6b**	70
3	**7a**	**8a**	89
4	**7b**	**8b**	82
5	**9a**	**10a**	87
6	**9b**	**10b**	79
7	**11a**	**12a**	82
8	**11b**	**12b**	80

[a] All reactions were performed in CH_2Cl_2 at −78 °C ⟶ room temp. with 2 equiv. TFA. All yields refer to chromatographically homogeneous material.

successful. As evident from TLC analysis of the reaction mixtures the formation of the corresponding *N*-sulfonylenamines **6a**, **b** was complete within a few minutes (CH_2Cl_2, −78 °C); however, all attempts to isolate these materials resulted in decomposition of the desired products and formation of several unidentified compounds. In contrast, dehydration of the compounds **5a**, **b** by trifluoroacetic acid (TFA) and subsequent work-up proceeded smoothly, yielding the corresponding *N*-sulfonylenamines **6a**, **b** in good yields as summarized in Table 1. β-Unsubstituted α-hydroxy *N*-sulfonylamines afforded the corresponding enamines in somewhat lower yields than the β-substituted analogues (compare entries 1, 2 *vs.* 3–8), due mainly to the greater stability of the more highly substituted *N*-sulfonylenamines towards silica gel chromatography. It is also interesting to note that the α-hydroxypyrrolidine derivatives gave slightly higher yields of the corresponding enamines than their α-hydroxypiperidine counterparts (Table 1, compare entries 1, 3, 5, 7 *vs.* 2, 4, 6, 8), although the differences are not significant enough to allow for any general conclusions.

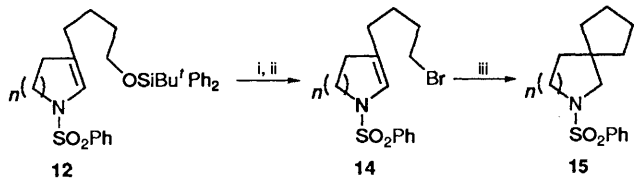
In the analogous *N*-acyliminium ion series it has been shown that, upon attempting to trap these intermediates with nucleophiles, the formation of the corresponding *N*-acylenamines can be an important side reaction.[6] It was suggested that the *N*-acylenamines were formed from the iminium ion intermediates and that this process may be reversible in an acidic medium.[7] As a consequence, we were interested to find out if the formation of *N*-sulfonylenamines would impose any limitations on the addition of carbon nucleophiles to *N*-sulfonyliminium ions. The addition of nucleophiles to β-unsubstituted cyclic *N*-sulfonyliminium ions **3a**, **b** (R = H) proceeds in good yield with no detectable formation of the corresponding enamines.[5] However, when β-substituted α-hydroxy *N*-sulfonylamines **7a**, **b** were treated with allyltrimethylsilane and a Lewis acid [$TiCl_4$, $Ti(OPr^i)_4$, $SnCl_4$ or $BF_3{\cdot}OEt_2$] or a proton acid (TFA or AcOH) under standard conditions (CH_2Cl_2, −78 °C ⟶ room temp.) *N*-sulfonylenamines **8a**, **b** were isolated as the major products (> 65%) along with only minor amounts of the expected α-allylated sulfonamides **13a**, **b** (< 10%). Assuming



13 a *n* = 1
b *n* = 2

that iminium ions are intermediates in these reactions, it seems reasonable to propose that, under the reaction conditions, enamines **8a**, **b** are both the kinetically, *i.e.* in the presence of Lewis acids, as well as the thermodynamically, *i.e.* in the presence of proton acids, preferred products.

During the last decade radical carbon–carbon bond-forming reactions have grown in importance.[8] An especially attractive feature of these transformations is the possibility of conducting intramolecular radical cyclizations by the reactions of a carbon-centred radical with an appropriately located C–C double bond.[9] The success of this reaction sequence, as well as the tandem version of it, has been amply demonstrated in a number of total syntheses of structurally complex natural products.[10] Although the use of cyclic enamines or enamides as the alkene part in these types of cyclizations would be an attractive entry to polycyclic alkaloids, the implementation of this strategy has only been scarcely documented,[11] probably because of the low reactivity of these olefins toward nucleophilic radicals.[12] As a consequence, we wanted to investigate if cyclic *N*-sulfonylenamines are useful as substrates in intramolecular radical cyclizations. In order to probe this, *N*-sulfonylenamines **12a**, **b** were converted into bromides **14a**, **b** by removal of the hydroxy protecting group[13] followed by bromination[14] (Scheme 2).



a *n* = 1, **b** *n* = 2

Scheme 2 *Reagents, conditions and yields:* i, Bu_4NF, THF, **a** 95%, **b** 93%; ii, CBr_4, Ph_3P, CH_2Cl_2, 0 °C, **a** 87%, **b** 87%; iii, Bu_3SnH, AIBN, C_6H_6, 80 °C, **a** 57%, **b** 54%

Upon treating compounds **14a**, **b** with Bu_3SnH (AIBN, benzene) under high dilution conditions,[15] the corresponding spirocyclic sulfonamides **15a**, **b** were obtained in good yields. Thus, we believe that the use of properly functionalized *N*-sulfonylenamines as substrates in intramolecular radical cyclizations should offer a novel entry to polycyclic alkaloids.

In conclusion, we have shown that five- and six-membered cyclic *N*-sulfonylenamines are readily available from the corresponding lactams by an efficient two step procedure. In addition, enamines **12a**, **b** were converted into the spirocyclic derivatives **15a**, **b**, the key transformation being an intramolecular radical cyclization, thus providing a novel entry to an interesting class of compounds.

Experimental

^1H and ^{13}C NMR spectra were obtained on a Varian XL-300 spectrometer using $CDCl_3$ ($CHCl_3$ δ 7.26) as solvent. *J* Values are given in Hz. IR spectra were run on a Perkin-Elmer 298 spectrophotometer and only the strongest/structurally most important peaks (ν/cm^{-1}) are listed. Flash chromatography employed Grace Amicon silica gel 60 (0.035–0.070 mm). Methylene chloride was distilled from calcium hydride immediately before use; tetrahydrofuran (THF) and benzene were distilled from sodium–benzophenone ketyl. All reactions were run in septum-capped, oven-dried flasks under an atmospheric pressure of nitrogen, solvents, reactant solutions and liquid reagents being transferred *via* oven dried syringes. Analytical data for *N*-sulfonylenamines **6a**, **b** are listed in ref. 5(*b*). α-Hydroxy *N*-sulfonylamines **7a**, **b**, **9a**, **b** and **11a**, **b** were prepared by alkylation[16] of the corresponding lactams followed by DIBAL reduction.[5b]

General Procedure for the Dehydration of α-Hydroxy N-*Sulfonylamines.*—To a stirred solution of the substrate (1 mmol)

in CH_2Cl_2 (5 cm^3) at −78 °C was added TFA (0.154 cm^3, 2.0 mmol). The reaction mixture was allowed to warm to room temperature (2 h), then solid K_2CO_3 was added and the resultant slurry stirred for an additional 30 min. Filtration, removal of the solvents and flash chromatography (EtOAc–heptane) gave the corresponding *N*-sulfonylenamines as indicated in Table 1.

3-*Methyl*-2-*pyrrolin*-1-*yl* p-*tolyl sulfone* **8a**. δ_H(300 MHz; $CDCl_3$) 7.66 (2 H, d, *J* 8.5), 7.31 (2 H, d, *J* 8.5), 6.56 (1 H, br s), 3.48 (2 H, t, *J* 9.0), 2.43 (3 H, s), 2.34 (2 H, br t, *J* 9.0) and 1.64 (3 H, br s); δ_C(75 MHz; $CDCl_3$) 143.6, 132.9, 129.6, 127.8, 124.7, 122.6, 47.7, 34.0, 21.6 and 13.5; ν(KBr)/cm^{-1} 2980, 2920, 1595, 1340 and 1160; m.p. 129–135 °C (Found: M^+, 237.0827. Calc. for $C_{12}H_{15}NO_2S$: M^+, 237.0824).

3,4-*Dihydro*-5-*methyl*-1(2H)-*pyridyl* p-*tolyl sulfone* **8b**. δ_H(300 MHz; $CDCl_3$) 7.65 (2 H, d, *J* 8.1), 7.29 (2 H, d, *J* 8.1), 6.41 (1 H, m), 3.31 (2 H, m), 3.30 (3 H, s), 1.81 (2 H, br t) and 1.68–1.51 (5 H, m); δ_C(75 MHz; $CDCl_3$) 143.3, 135.2, 129.6, 127.1, 119.5, 117.5, 43.4, 26.4, 21.5 and 21.0; ν(KBr)/cm^{-1} 3060, 2920, 1670, 1595, 1340 and 1160; m.p. 87–89 °C (Found: M^+, 251.0981. Calc. for $C_{13}H_{17}NO_2S$: M^+, 251.0980).

3-*Benzyl*-2-*pyrrolin*-1-*yl phenyl sulfone* **10a**. δ_H(300 MHz; $CDCl_3$) 7.79 (2 H, m), 7.65–7.49 (3 H, m), 7.30–7.19 (3 H, m), 7.06 (2 H, m), 6.11 (1 H, br s), 3.52 (2 H, t, *J* 8.9), 3.30 (2 H, br s) and 2.28 (2 H, br t, *J* 8.9); δ_C(75 MHz; $CDCl_3$) 138.3, 135.8, 132.9, 129.0, 128.5, 128.4, 127.7, 126.8, 126.5, 125.7, 47.8, 34.7 and 31.9; ν(KBr)/cm^{-1} 3100, 2900, 1660, 1600, 1360 and 1160; m.p. 101–105 °C (Found: M^+, 299.0981. Calc. for $C_{17}H_{17}NO_2S$: M^+, 299.0980).

5-*Benzyl*-3,4-*dihydro*-1(2H)-*pyridyl phenyl sulfone* **10b**. δ_H(300 MHz; $CDCl_3$) 7.79 (2 H, m), 7.63–7.48 (3 H, m), 7.21–7.16 (3 H, m), 7.09 (2 H, m), 6.59 (1 H, br s), 3.33 (2 H, m), 3.26 (2 H, s), 1.75 (2 H, br t, *J* 5.1) and 1.56 (2 H, m); δ_C(75 MHz; $CDCl_3$) 139.4, 138.8, 132.7, 129.1, 128.6, 128.4, 127.1, 126.3, 121.1, 43.7, 41.6, 24.2 and 20.8; ν(KBr)/cm^{-1} 3060, 2920, 1660, 1600, 1350 and 1160; m.p. 85–89 °C (Found: M^+, 313.1131. Calc. for $C_{18}H_{19}NO_2S$: M^+, 313.1136).

3-(tert-*Butyldiphenylsiloxybutyl*)-2-*pyrrolin*-1-*yl phenyl sulfone* **12a**. δ_H(300 MHz; $CDCl_3$) 7.79 (2 H, m), 7.62 (4 H, m), 7.60–7.33 (9 H, m), 6.06 (1 H, br s), 3.61 (2 H, t, *J* 5.7), 3.48 (2 H, t, *J* 9.0), 2.28 (2 H, br t, *J* 9.0), 1.94 (2 H, t, *J* 6.1), 1.49–1.39 (4 H, m) and 1.03 (9 H, s); δ_C(75 MHz; $CDCl_3$) 135.8, 135.6, 134.0, 132.8, 129.6, 129.0, 127.7, 127.6, 127.5, 124.2, 63.4, 47.6, 32.1, 31.9, 27.8, 26.9, 23.6, 19.2 and −5.2; ν(film)/cm^{-1} 3060, 2940, 1655, 1585 and 1350 (Found: M^+, 519.2254. Calc. for $C_{30}H_{37}NO_3SSi$: M^+, 519.2263).

5-(tert-*Butyldiphenylsiloxybutyl*)-3,4-*dihydro*-1(2H)-*pyridyl phenyl sulfone* **12b**. δ_H(300 MHz; $CDCl_3$) 7.78 (2 H, m), 7.67 (4 H, m), 7.56–7.32 (9 H, m), 6.43 (1 H, br s), 3.64 (2 H, t, *J* 7.9), 3.31 (2 H, t, *J* 5.6), 1.93 (2 H, t, *J* 7.1), 1.79 (2 H, t, *J* 5.9), 1.57 (2 H, m), 1.55–1.37 (4 H, m) and 1.07 (9 H, s); ν(film)/cm^{-1} 3060, 2935, 1660, 1585, 1350 and 1165 [Found: $(M + H)^+$, 534.2501. Calc. for $C_{31}H_{40}NO_3SSi$: $(M + H)^+$, 534.2498].

3-(4-*Bromobutyl*)-2-*pyrrolin*-1-*yl Phenyl Sulfone* **14a**.—To a solution of sulfonamide **12a** (326 mg, 0.628 mmol) in THF (5 cm^3) at 0 °C was added $Bu_4NF{\cdot}3H_2O$ (238 mg, 0.754 mmol). The resultant mixture was slowly warmed to room temperature and then poured into Et_2O–aq. $NaHCO_3$. The aqueous phase was separated and extracted once with Et_2O. The combined organic phases were washed once with brine, dried ($MgSO_4$) and then concentrated. Flash chromatography of the residue (EtOAc–heptane, 1 : 1 ⟶ 7 : 1) gave the corresponding alcohol as an oil (167 mg, 95%).

To a stirred solution of the alcohol from above (149 mg, 0.530 mmol) in CH_2Cl_2 (5 cm^3) at 0 °C was added triphenylphosphine (167 mg, 0.636 mmol) and carbon tetrabromide (202 mg, 0.610 mmol) and the resultant mixture was allowed to warm to room temperature. After 1 h the solvents were removed and the residue was subjected to flash chromatography (EtOAc–heptane, 1 : 4) to yield bromide **14a** as a colourless oil (159 mg, 87%); δ_H(300 MHz; $CDCl_3$) 7.79 (2 H, m), 7.61–7.44 (3 H, m), 6.09 (1 H, br s), 3.51 (2 H, t, *J* 8.9), 3.36 (2 H, t, *J* 7.9), 2.33 (2 H, br t, *J* 8.9), 2.03 (2 H, br t, *J* 8.0), 1.75 (2 H, m) and 1.49 (2 H, m); δ_C(75 MHz; $CDCl_3$) 135.7, 132.9, 129.0, 127.3, 126.5, 124.6, 47.5, 33.4, 32.1, 32.0, 27.2 and 25.8; ν(film)/cm^{-1} 3090, 2930, 1650, 1580, 1350 and 1165.

5-(4-*Bromobutyl*)-3,4-*dihydro*-1(2H)-*pyridyl phenyl sulfone* **14b**. Prepared as detailed above for compound **14a**; δ_H(300 MHz; $CDCl_3$) 7.77 (2 H, m), 7.60–7.47 (3 H, m), 6.44 (1 H, br s), 3.38 (2 H, t, *J* 6.7), 3.32 (2 H, m), 1.99 (2 H, t, *J* 6.9), 1.86–1.71 (4 H, m), 1.58 (2 H, m) and 1.50 (2 H, m); δ_C(75 MHz; $CDCl_3$) 137.8, 132.7, 129.1, 127.0, 120.7, 120.0, 43.6, 34.2, 33.5, 32.0, 26.0, 24.4 and 20.8; ν(film)/cm^{-1} 3060, 2930, 1670, 1580, 1350 and 1165.

Phenyl Pyrrolidine-3-*spirocyclopentan*-1-*yl Sulfone* **15a**.—To a solution of bromide **14a** (321 mg, 0.933 mmol) and AIBN (10 mg, 0.060 mmol) in refluxing benzene (15 cm^3) was added Bu_3SnH (0.376 cm^3, 1.400 mmol) and AIBN (10 mg, 0.060 mmol) in benzene (4 cm^3) over 5 h *via* a syringe pump. The reaction mixture was then cooled to room temperature, diluted with Et_2O (15 cm^3), treated with iodine until it turned brown, and then treated with DBU (0.977 cm^3, 6.532 mmol). The resultant heterogeneous mixture was filtered through a short pad of silica, the filter-cake was washed twice with Et_2O and the combined filtrate and washings were concentrated. Flash chromatography (EtOAc–heptane, 1 : 2) of the oily residue gave sulfonamide **15a** (140 mg, 57%); δ_H(300 MHz; $CDCl_3$) 7.82 (2 H, m), 7.64–7.49 (3 H, m), 3.32 (2 H, t, *J* 7.2), 3.09 (2 H, s), 1.65 (2 H, t, *J* 7.2), 1.60–1.51 (4 H, m) and 1.38–1.31 (4 H, m); δ_C(75 MHz; $CDCl_3$) 137.2, 132.5, 128.9, 127.3, 58.7, 49.8, 47.4, 37.4, 36.4 and 24.5; ν(film)/cm^{-1} 3060, 2950, 1350 and 1170 (Found: M^+, 265.1125. Calc. for $C_{14}H_{19}NO_2S$: M^+, 265.1136).

Phenyl Pyridine-3-*spirocyclopentan*-1-*yl Sulfone* **15b**.—Prepared as detailed above for compound **15a**; δ_H(300 MHz; $CDCl_3$) 7.76 (2 H, m), 7.62–7.47 (3 H, m), 2.95 (2 H, t, *J* 5.5), 2.68 (2 H, s), 1.74–1.55 (8 H, m) and 1.47–1.30 (4 H, m); δ_C(75 MHz; $CDCl_3$) 136.6, 132.5, 128.8, 127.5, 55.6, 46.6, 42.6, 36.5, 35.1, 24.6 and 22.8; ν(film)/cm^{-1} 3060, 2950, 1345 and 1175 (Found: M^+, 279.1295. Calc. for $C_{15}H_{21}NO_2S$: M^+, 279.1293).

Acknowledgements

This work was supported financially by the Swedish Natural Science Research Council and Kungliga Fysiografiska Sällskapet i Lund. We are grateful to Dr. David Tanner for linguistic improvements to the manuscript and to Mr. Herman Lindborg for constructing the syringe pump.

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Paper 3/06056J
Received 11*th October* 1993
Accepted 22*nd December* 1993