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# Synthesis of Substituted Piperidines, Indolizidines, Quinolizidines, and Pyrrolizidines via a Cycloaddition Strategy Using Acetylenic Sulfones as Alkene Dipole Equivalents

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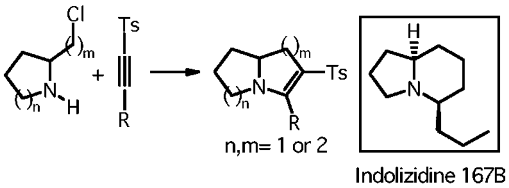
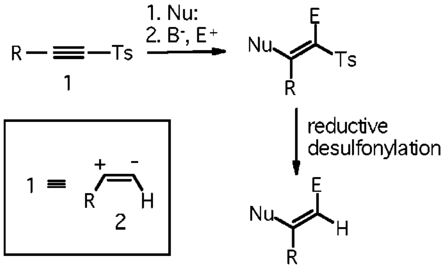
## ABSTRACT



**The conjugate additions of *β*- and *γ*-chloroamines to acetylenic sulfones afford enamine sulfones, which then undergo intramolecular alkylation to produce the corresponding cyclic enamines. This provides a convenient route to substituted piperidines, indolizidines, quinolizidines, and pyrrolizidines. The enantioselective total synthesis of the alkaloid (−)-indolizidine 167B (also named gephyrotoxin 167B) was thus achieved by the cycloaddition of (*S*)-2-(2-chloroethyl)pyrrolidine to 1-(*p*-toluenesulfonyl)-1-pentyne, followed by stereoselective reduction of the enamine moiety and reductive desulfonylation.**

Acetylenic sulfones **1** are readily available compounds with numerous synthetic applications.[1] For example, the electron-withdrawing sulfone group activates the acetylene moiety toward conjugate additions to afford *β*-substituted vinyl sulfones. Furthermore, vinyl sulfones can be deprotonated in the α-position,[2] thus permitting the introduction of electrophiles via the corresponding sulfone-stabilized anions. Finally, the sulfone moiety can be removed at the end of a synthetic sequence by various reductive desulfonylation techniques.[3] The possibility of employing these three operations sequentially suggested the use of acetylenic sulfones as the synthetic equivalents of hypothetical alkene dipole species **2**, where the sulfone functionality acts as a disposable activating group (Scheme 1). An intramolecular version of

**Scheme 1**



Scheme 1 was envisaged as the basis of a novel cyclization strategy. We now report that acetylenic sulfones undergo conjugate additions with *β*- and *γ*-chloro-substituted second-

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(1) (a) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993. (b) Tanaka, K.; Kaji, A. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; Wiley: Chichester, 1988; Chapter 15.

(2) (a) Eisch, J. J.; Galle, J. E. *J. Org. Chem.* **1979**, *44*, 3279. (b) Kleijn, H.; Vermeer, P. *J. Organomet. Chem.* **1986**, *302*, 1. (c) Nájera, C.; Yus, M. *J. Org. Chem.* **1988**, *53*, 4708. (d) McCombie, S. W.; Shankar, B. B.; Ganguly, A. K. *Tetrahedron Lett.* **1987**, *28*, 4123. (e) Pelter, A.; Ward, R. S.; Little, G. M. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2775. (f) Caturla, F.; Nájera, C. *Tetrahedron* **1997**, *53*, 11449.

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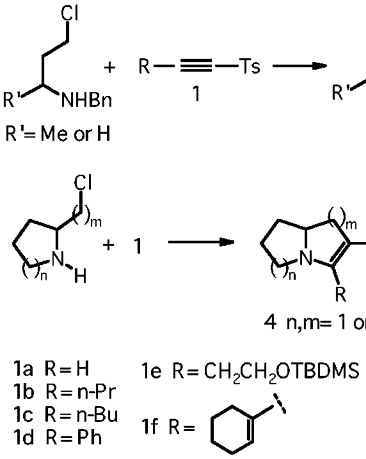
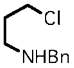
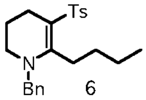
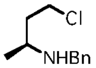
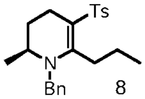
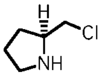
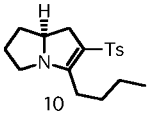
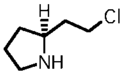
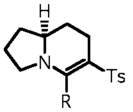
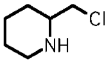
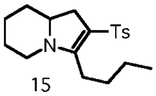
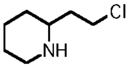
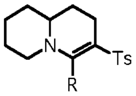
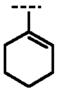
ary amines[4] to produce enamine sulfones, which undergo intramolecular alkylation when deprotonated with LDA to afford cyclized products **3** and **4**, as shown in Scheme 2.[5] A concise and convenient approach to substituted piperidines, quinolizidines, indolizidines, and pyrrolizidines is thus made possible. These general types of structures are found widespread in nature in the corresponding classes of alkaloids,[6] as well as in numerous synthetic analogues. Their biological and medicinal properties provide added incentive for the development of versatile new synthetic strategies for their preparation.

**Scheme 2**



The cyclizations of chloroamines **5**, **7**, **9**, **11**, **14**, and **16** with acetylenic sulfones **1a**−**1f** to afford products **6**, **8**, **10**, **12**, **13**, **15**, and **17**−**21** are shown in Table 1. The required chloroamines[7] were easily obtained by chlorination of the corresponding amino alcohols with thionyl chloride. The amino alcohols were in turn obtained either commercially or by the reduction of esters of the corresponding amino acids. The $\gamma$-chloro analogues **7** and **11** required Arndt−Eistert homologation[8] of the corresponding $\alpha$-amino acids prior to reduction. The chloroamines were isolated and stored as their hydrochloride salts, which are stable and easily handled. The acetylenic sulfones **1a**−**1f** were obtained by selenosulfonation methodology.[9]

**Table 1.** Cyclizations of $\beta$- and $\gamma$-Chloroamines with Acetylenic Sulfones

| Entry | Chloro-amine | Acetylenic sulfone | Product | Yield (%) |
|---|---|---|---|---|
| 1 | <br>5 | 1c | <br>6 | 94 |
| 2 | <br>7 | 1b | <br>8 | 88 |
| 3 | <br>9 | 1c | <br>10 | 75 |
|  |  |  |  |  |
| 4 | 11 | 1b | 12 R = n-Pr | 94 |
| 5 | 11 | 1c | 13 R = n-Bu | 86 |
| 6 | <br>14 | 1c | <br>15 | 77 |
|  |  |  |  |  |
| 7 | 16 | 1a | 17 R = H | 64 |
| 8 | 16 | 1c | 18 R = n-Bu | 84 |
| 9 | 16 | 1d | 19 R = Ph | 78 |
| 10 | 16 | 1e | 20 R = CH$_2$CH$_2$OTBDMS | 81 |
| 11 | 16 | 1f | 21 R =  | 80 |

Typically, the conjugate addition reactions were performed by stirring the freshly liberated free chloroamine with the

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(3) See ref 1a, Chapter 9, and Grossert, J. S. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; Wiley: Chichester, 1988; Chapter 20.

(4) For other examples of conjugate additions of nitrogen nucleophiles to acetylenic sulfones, see: (a) Back, T. G.; Bethell, R. J.; Parvez, M.; Wehrli, D. *J. Org. Chem*. **1998**, *63*, 7908. (b) Truce, W. E.; Brady, D. G. *J. Org. Chem*. **1966**, *31*, 3543. (c) Truce, W. E.; Markley, L. D. *J. Org. Chem*. **1970**, *35*, 3275. (d) Truce, W. E.; Onken, D. W. *J. Org. Chem*. **1975**, *40*, 3200. (e) Stirling, C. J. M. *J. Chem. Soc*. **1964**, 5863. (f) McMullen, C. H.; Stirling, C. J. M. *J. Chem. Soc. B* **1966**, 1217. (g) McDowell, S. T.; Stirling, C. J. M. *J. Chem. Soc. B* **1967**, 351. (h) Cossu, S.; De Lucchi, O.; Durr, R. *Synth. Commun*. **1996**, *26*, 4597. (i) Cinquini, M.; Cozzi, F.; Pelosi, M. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1430.

(5) An intramolecular acylation reaction of an enamine sulfone derived from a primary amine was recently exploited in the synthesis of pumiliotoxin C: Back, T. G.; Nakajima, K. *J. Org. Chem*. **1998**, *63*, 6566. To our knowledge, no cyclizations of enamine sulfones derived from cyclic amines have been reported, as are required for the introduction of nitrogen at a ring-fusion site in products **4**.

(6) For lead references, see the following. Piperidine alkaloids: (a) Strunz, G. M.; Findlay, J. A. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1985; Vol. 26, pp 89−183. (b) Fodor, G. B.; Colasanti, B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 1−90. Indolizidine and quinolizidine alkaloids: (c) Howard, A. S.; Michael, J. P. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1986; Vol. 28, pp 183−308. (d) Herbert, R. B. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1985; Vol. 3, pp 241−274. Pyrrolizidine alkaloids: (e) Wróbel, J. T. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: Orlando, 1985; Vol. 26, pp 327−384. For a list of other reviews of these classes of alkaloids, see: (f) Dewick, P. M. *Medicinal Natural Products*; Wiley: Chichester, 1997; pp 371−374.

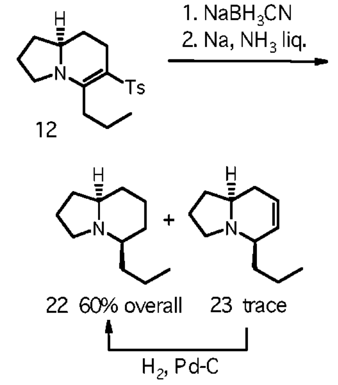
(7) The chloroamines were prepared by the following procedures. (a) **5**: Dolfini, J. E.; Dolfini, D. M. *Tetrahedron Lett.* **1964**, 2103. (b) **9**: Piper, J. R.; Johnston, T. P. *J. Org. Chem*. **1963**, *28*, 981. (c) For a similar procedure leading to racemic **11** from the corresponding racemic amino alcohol, see: Neth. Appl. Patent 6,600,184; July, 13, 1966; *Chem. Abstr.* **1967**, *66*, 2580r. (d) **14** and **16**: Norton, T. R.; Seibert, R. A.; Benson, A. A.; Bergstrom, F. W. *J. Am. Chem. Soc.* **1946**, *68*, 1572. (e) Chloroamine **7** was prepared from methyl (*S*)-3-(*N*-benzoylamino)butanoate by reduction with lithium aluminum hydride and chlorination with thionyl chloride.

(8) For lead references, see: March, J. In *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; pp 1083−1085.

acetylenic sulfone in THF or dichloromethane at room temperature or under reflux. The resulting enamine sulfone in THF was then added to excess LDA in THF at −78 °C to effect cyclization. The yields in Table 1 refer to isolated products, which were fully characterized (IR, $^1$H and $^{13}$C NMR, MS, and either HRMS or elemental analyses).[10,11]

Table 1 shows that this cyclization technique provides straightforward access to 2- or 2,6-disubstituted piperidines (entries 1 and 2), 3-substituted pyrrolizidines (entry 3), 5- or 3-substituted indolizidines (entries 4−5 and 6, respectively), and 4-substituted quinolizidines (entries 7−11) that are additionally functionalized as enamine sulfones. Since the starting chloroamines can be obtained as pure enantiomers from the corresponding amino acids, the method can be employed in the enantioselective preparation of the corresponding cycloadducts (entries 2−5). Moreover, the enamine sulfone moiety in the products is amenable to further synthetic transformations, which are under current investigation. For example, product **12** from entry 4 was converted enantioselectively into the naturally occurring alkaloid (−)-indolizidine **167B** (also named gephyrotoxin **167B**) (**22**)[12−14] in 60% overall yield by stereoselective reduction of the enamine function with sodium cyanoborohydride,[15] followed by reductive desulfonylation with sodium in liquid ammonia.[16] Catalytic hydrogenation of the crude product then reduced a small amount (ca. 5%) of the unsaturated byproduct **23** that was formed by competing elimination of the sulfone group during the desulfonylation step (Scheme 3).

**Scheme 3**



These preliminary results demonstrate that acetylenic sulfones act as alkene dipole equivalents and provide the basis of a useful and versatile cyclization protocol with secondary $\beta$- or $\gamma$-chloroamines, thus affording access to a wide range of nitrogen heterocycles.

**Acknowledgment.** We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support.

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(9) The following acetylenic sulfones were prepared by literature methods. For **1a**, see: (a) Chen, Z.; Trudell, M. L. *Synth. Commun*. **1994**, *24*, 3149. (b) Back, T. G.; Collins, S.; Kerr, R. G. *J. Org. Chem*. **1983**, *48*, 3077. For **1b**: see ref 5. For **1c**, see ref 9b and (c) Back, T. G.; Krishna, M. V. *J. Org. Chem*. **1987**, *52*, 4265. For **1d**, see ref 9b. For **1f**, see: (d) Back, T. G.; Lai, E. K. Y.; Muralidharan, K. R. *J. Org. Chem*. **1990**, *55*, 4595. Compound **1e** was prepared via the general method of ref 9b, from the selenosulfonation of 3-butyn-1-ol, followed by protection as the *tert*-butyldimethylsilyl ether and selenoxide elimination.

(10) In a typical example, chloroamine **11** was liberated from its hydrochloride (4.75 mmol) with aqueous KOH just prior to use. The free base and acetylene **1b** (3.98 mmol) were stirred in dichloromethane for 5 h at room temperature. The solvent was evaporated in vacuo, the residue was dissolved in THF and added to excess LDA (8 mmol) in THF at −78 °C, and the mixture was stirred for 2 min. The reaction was quenched by filtration of the solution through basic alumina. The product was isolated by chromatography on silica gel (elution with 20% ethyl acetate−hexanes) to afford 94% (based on **1b**) of **12** as white crystals: mp 95−96 °C (from dichloromethane−hexanes): IR (KBr) 1551, 1318, 1282, 1123, 1081 cm$^{-1}$; $^1$H NMR (200 MHz) $\delta$ 7.72 (d, $J$ = 8.2 Hz, 2 H), 7.24 (d, $J$ = 8.4 Hz, 2 H), 3.58−3.42 (m, 1 H), 3.40−3.15 (m, 2 H), 2.98−2.78 (m, 1 H), 2.68−2.22 (m, 3 H), 2.39 (s, 3 H), 2.21−2.00 (m, 2 H), 1.99−1.09 (m, 6 H), 0.97 (t, $J$ = 7.4 Hz, 3 H); $^{13}$C NMR (50 MHz) $\delta$ 154.6, 142.2, 141.4, 128.9, 125.8, 97.0, 57.9, 46.9, 32.0 (2 signals), 27.4, 25.1, 23.6, 22.3, 21.2, 14.2; mass spectrum, *m*/*z* (relative intensity, %) 319 (M$^+$, 40), 227 (91), 164 (100), 91 (68), 41 (67). Anal. Calcd for $C_{18}H_{25}NO_2S$: C, 67.67; H, 7.89; N, 4.38. Found: C, 67.91; H, 7.80; N, 4.42. $[\alpha]^{20}_D$ −246.7 (*c* 1.12, $CHCl_3$).

(11) In general, a small excess (10−20%) of the chloroamine hydrochloride was employed to compensate for possible losses during the liberation of the corresponding free base, which was generally used immediately and without purification. The yields in Table 1 were thus calculated on the basis of the acetylenic sulfone. When the preparation of **12** was repeated with equimolar amounts of the hydrochloride of **11** and **1b**, the yield of **12** was 84%.

(12) Product **22** is a dendrobatid alkaloid found in the toxic skin secretions of certain species of neotropical frogs. For a general review of these compounds, see: Daly, J. F.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Wiley: New York, 1986; Vol. 4, pp 1−274.

(13) For previous syntheses of (−)-indolizidine **167B**, see: (a) Weymann, M.; Pfrengle, W.; Schollmeyer, D.; Kunz, H. *Synthesis* **1997**, 1151. (b) Angle, S. R.; Henry, R. M. *J. Org. Chem*. **1997**, *62*, 8549. (c) Lee, E.; Li, K. S.; Lim, J. *Tetrahedron Lett*. **1996**, *37*, 1445. (d) Fleurant, A.; Saliou, C.; Célérier, J. P.; Platzer, N.; Moc, T. V.; Lhommet, G. *J. Heterocycl. Chem*. **1995**, *32*, 255. (e) Jefford, C. W.; Wang, J. B. *Tetrahedron Lett*. **1993**, *34*, 3119. (f) Jefford, C. W.; Tang, Q.; Zaslona, A. *J. Am. Chem. Soc*. **1991**, *113*, 3513. (g) Polniaszek, R. P.; Belmont, S. E. *J. Org. Chem*. **1990**, *55*, 4688.

(14) **Procedure for the Preparation of 22.** Trifluoroacetic acid (1.0 mL, 13 mmol) was added dropwise to a suspension of **12** (1.32 mmol) and $NaBH_3CN$ (13.3 mmol) in 15 mL of dichloromethane, and the mixture was stirred at room temperature for 30 min and refluxed for 30 min. It was washed with aqueous KOH, dried ($MgSO_4$), and concentrated in vacuo to provide a yellow oil. This was dissolved in 30 mL of liquid ammonia, sodium (40 mmol) was added, and the mixture was stirred at −33 °C for 15 min. Solid $NH_4Cl$ was added, and the ammonia was allowed to evaporate. The residue was dissolved in 10% HCl and washed with ether. The aqueous layer was basified with KOH, and the product was extracted with ether, dried ($MgSO_4$), and concentrated in vacuo to provide the crude product, containing ca. 5% of **23** (tentative assignment based on its NMR spectrum). The mixture was hydrogenated at 1 atm in 4 mL of ethanol with 10% Pd−C at room temperature and for 1 h. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo. The residue was treated with 1 M HCl−ether (3.0 mL, 3.0 mmol), and the resulting solid was recrystallized from ethanol−ether, basified with aqueous KOH, extracted with dichloromethane, dried ($MgSO_4$), and concentration in vacuo to afford 132 mg (60%) of (−)-indolizidine **167B** (**22**) as a yellow oil: $^1$H NMR (200 MHz) $\delta$ 3.26 (dt, $J$ = 8.3, 2.2 Hz, 1 H), 2.05−1.55 (m, 10 H), 1.54−1.02 (m, 7 H), 0.90 (t, $J$ = 7.1 Hz, 3 H); $^{13}$C NMR (50 MHz) $\delta$ 64.9, 63.6, 51.5, 36.8, 30.9, 30.8, 30.5, 24.6, 20.3, 19.0, 14.4; mass spectrum, *m*/*z* (relative intensity, %) 167 (M$^+$, 4), 124 (100), 96 (22). $[\alpha]^{20}_D$ −106.9 (*c* 1.10, $CH_2Cl_2$), lit.[13b] $[\alpha]^{25}_D$ −116.6 (*c* 0.0042, $CH_2Cl_2$), lit.[13c] $[\alpha]^{24}_D$ −112 (*c* 1.25 $CH_2Cl_2$), lit.[13d] $[\alpha]^{20}_D$ −115 (*c* 1.16, $CH_2Cl_2$), lit.[13g] $[\alpha]_D$ −111.3 (*c* 1.3, $CH_2Cl_2$).

(15) For a general procedure for reducing other enamines with $NaBH_3CN$−TFA, see: Comins, D. L.; Weglarz, M. A. *J. Org. Chem*. **1991**, *56*, 2506.

(16) For a general procedure for reductive desulfonylation with Na−liquid $NH_3$, see: Marshall, J. A.; Cleary, D. G. *J. Org. Chem*. **1986**, *51*, 858.