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# A general synthetic route to 1-azabicyclo[*m.n.*0]alkenes *via* cyclisation based on α-sulfinyl carbanions

**Manat Pohmakotr,* Pornthep Numechai, Saisuree Prateeptongkum, Patoomratana Tuchinda and Vichai Reutrakul**

*Department of Chemistry, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand. E-mail: scmpk@mahidol.ac.th; Fax: +66(0)2644-5126*

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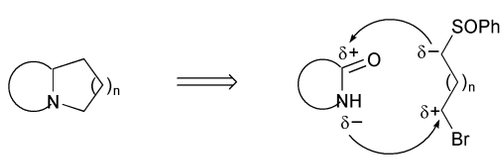
**The intramolecular nucleophilic addition of α-sulfinyl carbanions derived from the corresponding sulfinyl lactams afforded 1-azabicyclo[*m.n.*0]alkenes in good yields.**

The 1-azabicyclo[*m.n.*0]alkane framework is an important structural assembly in a number of heterocyclic systems, especially alkaloid natural products possessing biological activities such as pyrrolidine,[1,2] indolizidine and quinolizidine alkaloids,[3,4] and (−)-tuberostemonine.[5,6] Despite the fact that various synthetic strategies have been developed for these classes of compounds, an efficient, general construction is still regarded as an important synthetic challenge.

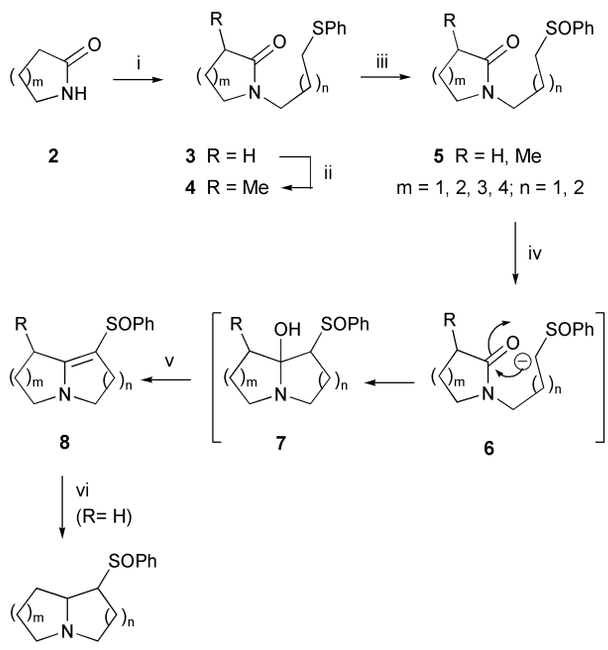
Our ongoing interest in cyclisation reactions based on α-sulfinyl carbanion[7] prompted us to search for a general entry to 1-azabicyclo[*m.n.*0]alkanes **1** starting from simple lactams. As shown in Fig. 1, it occurred to us that the construction of a framework such as **1** should be achievable by annulation onto lactams **2** by consecutive N–C and C–C bond formations employing 3-bromo-1-phenylsulfinylpropane and 4-bromo-1-phenylsulfinylbutane as 3- and 4-carbon building blocks for 1,3- and 1,4-dipole moieties, respectively. In this communication, we report our preliminary results for the preparation of 1-azabicyclo[*m.n.*0]alkanes **1** utilizing such a concept. Thus, *N*-phenylthioalkylation of lactam **2** with 3-phenylsulfanyl-1-bromopropane or 4-phenylsulfanyl-1-bromobutane employing NaH in *N*,*N*-dimethylformamide (DMF) at 0 °C to rt afforded sulfides **3** (Scheme 1).




**1** n = 1, 2 **2**

**Fig. 1**

Conversion of the sulfides **3a** and **3b** to the corresponding sulfides **4a** and **4b** could be accomplished by lithiation with lithium diisopropylamide (LDA, 1.1 equiv.) in tetrahydrofuran (THF) at −78 °C, followed by treatment with methyl iodide (1.1 equiv., −78 to 0 °C, overnight). The sulfides **3** and **4** were then oxidized with $NaIO_4$ in aqueous methanol at 0 °C to provide the requisite sulfoxides **5a–f** in good yields as listed in Table 1. The study for the cyclisation of the sulfoxides **5** to 1-azabicyclic compound **8** was carried out with compound **5a** to find the optimum conditions. It was found that cyclisation of **5a** to **8a** could be smoothly effected by employing lithium hexamethyldisilazide (LiHMDS) (1.1 to 2.0 equiv.) in tetrahydrofuran (THF) at −78 °C to rt (overnight), the expected product **8a**[8] could be obtained in 85–90% yield after column chromatography on silica gel. The use of lithium diisopropylamide as a base for the cyclisation under the same conditions afforded less satisfactory results. It was evident that the initially




**2** **3** R = H, **4** R = Me, **5** R = H, Me; m = 1, 2, 3, 4; n = 1, 2; **8**, **7**, **6**

**9** m = 2, 3; n =1

**Scheme 1** *Reagents and conditions*: (i) NaH, DMF, $BrCH_2(CH_2)_n$-$CH_2SPh$, 0 °C to rt, overnight; (ii) LDA, THF, −78 °C; then $CH_3I$, −78 °C to rt, overnight; (iii) $NaIO_4$, aq. MeOH, 0 °C, overnight; (iv) LiHMDS, THF, −78 °C to rt, overnight, then quenched with $H_2O$; (v) $-H_2O$; (vi) $NaBH_4$, MeOH, 5–10 °C, 2 h.

formed α-sulfinyl carbanion **6** underwent intramolecular nucleophilic addition to the carbonyl group of the lactam moiety to provide an intermediate **7** after quenching the reaction with water. Elimination of a water molecule from **7** gave 1-azabicyclic compound **8**.

As summarized in Table 1 (entries 1–6),[9] 1-azabicyclic compounds **8a–f** could be synthesized in good yields. Cyclisation of **5g** and **5h** under the standard conditions proceeded cleanly to the expected products of type **8** as indicated by TLC and $^1H$ NMR analyses of the crude products. However, purification of these cyclised products was troublesome and low yields were obtained due to decomposition at rt. Therefore, the crude products were further subjected to reduction by using $NaBH_4$ in methanol to **9a** and **9b** in 65 and 68% yields, respectively. We considered that the presence of the sulfoxide group in compounds **8** and **9** would lead to synthetic manipulation on various 1-azabicyclic skeletons.

In summary, we have demonstrated a new general strategy to 1-azabicyclo[*m.n.*0]-alkenes and -alkanes *via* the intramolecular nucleophilic addition of α-sulfinyl carbanion to the carbonyl group of lactam ring. This method provided not only a convenient 3-carbon and 4-carbon annulation onto lactams, but also the facile introduction of an α-substituent onto the

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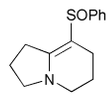
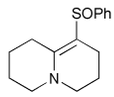
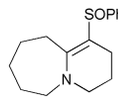
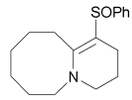
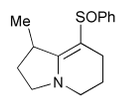
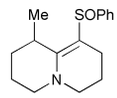
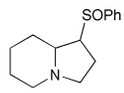
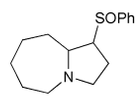
**Table 1** Preparation of 1-azabicyclic compounds **8** and **9**

| Entry | Lactam **2** | Sulfide **3** or **4** (%)[a,b] | Sulfoxide **5** (%)[a,b] | *m*, *n* in **3**, **4** and **5** | Products **8** and **9** (%)[a,b] | |
|---|---|---|---|---|---|---|
| 1 |  | **3a** (85%) | **5a**, R = H (95%) | *m* = 1, *n* = 2 |  | **8a** (85–90%) |
| 2 |  | **3b** (80%) | **5b**, R = H (95%) | *m* = 2, *n* = 2 |  | **8b** (89%) |
| 3 |  | **3c** (85%) | **5c**, R = H (92%) | *m* = 3, *n* = 2 |  | **8c** (87%) |
| 4 |  | **3d** (80%) | **5d**, R = H (94%) | *m* = 4, *n* = 2 |  | **8d** (85%) |
| 5 |  | **4a** (81%) | **5e**, R = Me (96%) | *m* = 1, *n* = 2 |  | **8e** (85%)[c] |
| 6 |  | **4b** (80%) | **5f**, R = Me (95%) | *m* = 2, *n* = 2 |  | **8f** (87%)[c] |
| 7 |  | **3e** (87%) | **5g**, R = H (86%) | *m* = 2, *n* = 1 |  | **9a** (65%)[c,d] |
| 8 |  | **3f** (74%) | **5h**, R = H (86%) | *m* = 3, *n* = 1 |  | **9b** (68%)[c,d] |

[a] Isolated yields by column chromatography ($SiO_2$, 2% MeOH in EtOAc containing 0.2% $NH_4OH$ solution). [b] All compounds were characterized by $^1H$ NMR, $^{13}C$ NMR, IR, MS, and elemental analyses or HMRS. [c] Obtained as a mixture of diastereomers. [d] Overall yields based on compounds **5g** and **5h**.

original lactam ring, the structural feature found in many natural products.

Furthermore, the developed strategy should provide a general solution for the syntheses of various classes of 1-azabicyclic alkaloids, such as indolizidines and quinolizidines. Extension of this methodology is currently under investigation and will be reported in due course.

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9 *Typical procedure for preparation of 1-azabicyclic compound* **8a**: A solution of **5a** (0.7691 g, 3.0 mmol) in THF (5 $cm^3$) was added dropwise to a cooled (−78 °C) THF (20 $cm^3$) solution of LHMDS [3.3 mmol, prepared by reacting hexamethyldisilazane (0.75 $cm^3$, 3.6 mmol) with *n*BuLi (2.2 $cm^3$, 3.3 mmol, 1.49 M in hexane) at −78 °C]. The resulting mixture was stirred and slowly warmed up to rt (14 h). The resulting pale yellow solution was quenched with water (7 $cm^3$) and extracted with ethyl acetate (3 × 50 $cm^3$). The combined organic extracts were washed with water, then brine and dried over anhydrous $Na_2SO_4$. The crude product was purified by column chromatography

(silica gel, 2% methanol in ethyl acetate containing 0.2% $NH_4OH$ solution) to afford **8a** (0.6307 g, 85% yield) as a pale yellow liquid. HRMS ($FAB^+$) found: 247.1025, $C_{14}H_{17}NOS$ requires 247.1027; IR $\nu_{max}$ (film)/$cm^{-1}$: 3049, 2925, 2855, 1613, 1579, 1496, 1442, 1352, 1296, 1211, 1198, 1129, 1092, 1079, 1020, 996, 913, 930, 888, 817, 750, 693; $^1H$ NMR $\delta_H$ (300 MHz; $CDCl_3$; $Me_4Si$): 7.48, 7.36 and 7.28 (each m, 5H, Ar*H*), 3.24 and 3.03 [each m, 5H, 2 × C*H*$_2$N and CH*H*C(N)=C], 2.85 [dt, *J* 16, 8 Hz, 1H, C*H*HC(N)=C], 2.21 [dt, *J* 14.9, 6 Hz, 1H, CH*H*C=C(N)], 1.92 [quint, *J* 7.3 Hz, 2H, C*H*$_2$CH$_2$C(N)=C], 1.72 [m, 2H, C*H*$_2$CH$_2$C=C(N)], 1.49 [m, 1H, C*H*HCC=C(N)]. $^{13}C$ NMR $\delta_C$ (75 MHz; $CDCl_3$; $Me_4Si$) 155.30, 144.35, 128.91, 128.37, 124.92, 95.54, 52.62, 44.40, 29.31, 21.52, 21.15, 16.37. MS: *m*/*z* (EI) 248 ($M^+ + 1$, 3%), 231 (4%), 199 (67%), 170 (51%), 120 (100%), 108 (6%), 92 (8%), 80 (5%), 77 (4%), 65 (5%).