

Synthesis and rearrangement of a bridged thioamide

Michal Szostak and Jeffrey Aubé*

*Department of Medicinal Chemistry, 1251 Wescoe Hall Drive, Malott Hall, Room 4070,
University of Kansas, Lawrence, Kansas 66045-7582*

jaube@ku.edu

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Corresponding Author:

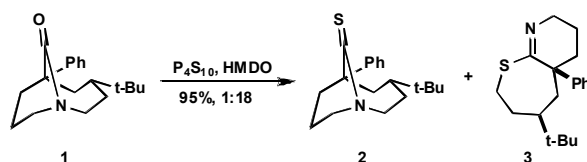
Professor Jeffrey Aubé*
Department of Medicinal Chemistry
1251 Wescoe Hall Drive
Malott Hall, Room 4070
University of Kansas
Lawrence, Kansas 66045-7582

Tel: 1.785.864.4496
Fax: 1.785.864.5326
E-mail: jaube@ku.edu

List of Known Compounds

The following compounds are known: lactams **1**, **4**.¹ Spectra of lactams **1** and **4** are reproduced from Ref. 1.

Thionation of lactam **1**



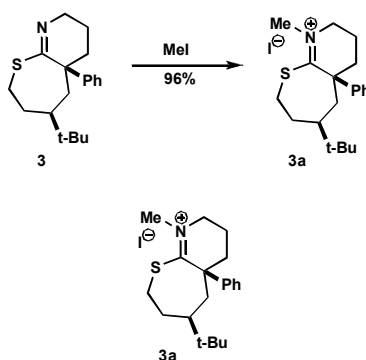
4-tert-Butyl-6-phenyl-1-azabicyclo[4.3.1]decane-10-thione (2) and 4-tert-Butyl-5a-phenyl-2,3,4,5,5a,6,7,8-octahydrothiepine[2,3-b]pyridine (3). 25 ml round bottom flask was charged with amide **1** (0.0200 g, 0.07 mmol, 1.0 equiv), P_4S_{10} (0.0080 g, 0.018 mmol, 0.25 equiv) and toluene (5.0 mL). After the reaction mixture was stirred at rt for 10 min, hexamethyldisiloxane (0.026 mL, 0.12 mmol, 1.7 equiv) was added and the reaction was heated at 90 °C for 22 h. After the reaction was cooled to rt, the solvent was removed and the reaction mixture was purified by chromatography (1/1 EtOAc/hexanes followed by 1/10/90 NH_3 /MeOH/ CH_2Cl_2) to afford **2** (R_f = 0.52, 1/4 EtOAc/hexanes) as oil (yield 5%, 0.0010 g, 0.0033 mmol) and **3** (R_f = 0.63, 1/10/90 NH_3 /MeOH/ CH_2Cl_2) as oil (yield 90%, 0.0189 g, 0.063 mmol). Compound **2**: 1H NMR (400 MHz, $CDCl_3$) δ 0.90 (s, 9H), 1.44 (q, J = 11.0 Hz, 1H), 1.68-1.77 (m, 2H), 1.90-2.02 (m, 3H), 2.17 (d, J = 10.1 Hz, 1H), 2.33-2.42 (m, 1H), 2.49 (d, J = 11.9 Hz, 1H), 3.03-3.11 (m, 1H), 3.44-3.52 (m, 1H), 3.72 (d, J = 12.2 Hz, 1H), 4.39 (dd, J = 7.2, 13.4 Hz, 1H), 7.22-7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 22.2, 27.1, 33.2, 37.6, 41.8, 46.3, 54.0, 57.5, 65.0, 125.1, 127.2, 127.5, 149.1, 225.5; IR (neat) 2955, 2918, 2851, 1491, 1445, 1367, 1315, 1180, 1080, 1070, 1047 cm^{-1} ; HRMS calcd for $C_{19}H_{28}NS$ ($M^+ + H$) 302.1942, found 302.1955. Compound **3**: 1H NMR (400 MHz, $CDCl_3$) δ 0.96 (s, 9H), 1.26-1.48 (m, 2H), 1.60 (m, 2H), 1.84 (d, J = 13.0 Hz, 1H), 1.94-2.14 (m, 4H), 2.49 (dt, J = 4.6, 14.8 Hz, 1H), 2.85 (m, 1H), 3.58-3.69 (m, 1H), 3.86 (ddt, J = 1.6, 5.4, 18.0 Hz, 1H), 7.22-7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 27.4, 29.8, 32.0, 33.6, 39.8, 41.1, 43.9, 51.4, 51.8, 126.5, 126.9, 128.3, 146.4, 173.0; IR (neat) 2941, 2866, 2212, 1670, 1605, 1477, 1445, 1366, 1126, 1061 cm^{-1} ; HRMS calcd for $C_{19}H_{28}NS$ ($M^+ + H$) 302.1942, found 302.1932.

Table 1. Influence of additional reaction conditions on product distribution.

Entry	Reagents	Conditions	2:3	Yield [%]
1	P ₁₀ S ₁₀ /HMDO (0.25/1.7 equiv)	Toluene, 90 °C, 6 h	<5:95	79 ^a
2	P ₁₀ S ₁₀ /HMDO (0.25/1.7 equiv)	Toluene, 90 °C, 3 h	n.a.	13 ^b
3	P ₁₀ S ₁₀ /HMDO (1.3/7.5 equiv)	Toluene, 90 °C, 15 h	<5:95	93 ^a
4	P ₁₀ S ₁₀ /HMDO (1.3/7.5 equiv)	Toluene, 90 °C, 2 h	1:3	40 ^c
5	P ₁₀ S ₁₀ (5.0 equiv)	Toluene, 90 °C, 15 h	<5:95	76 ^a

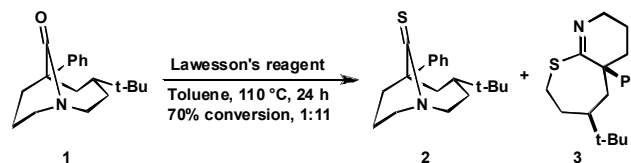
^aIsolated yield of **3**; ^bisolated yield of **2**; ^ccombined yield; n.a. = not available; <5:95 indicates that **2** was not observed by ¹H NMR of the crude reaction mixture. Note: no conversion was observed at lower temperatures, or in CH₂Cl₂, THF solvents.

Conversion of **3** to **3a**

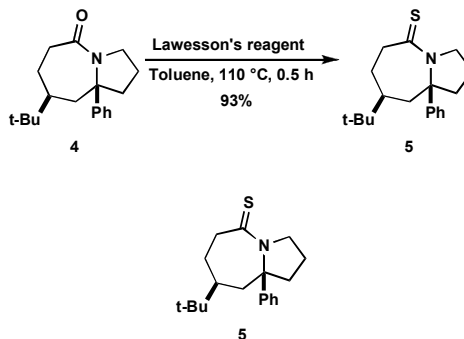


4-tert-Butyl-9-methyl-5a-phenyl-2,3,4,5,5a,6,7,8-octahydrothiepin[2,3-b]pyridin-9-ium iodide (3a). To a solution of **3** (0.0308 g, 0.10 mmol, 1.0 equiv) in CH₂Cl₂ (6.0 mL), MeI (0.13 mL, 2.0 mmol, 20.0 equiv) was added at rt, and the resulting reaction mixture was stirred at rt for 24 h. The solvent was removed to afford the title compound as yellow solid. Yield 96% (0.0434 g, 0.098 mmol). Recrystallization from CHCl₃ provided needles suitable for x-ray crystallography (m.p. = 167-8 °C). ¹H NMR (400 MHz, CDCl₃) δ 1.00 (s, 9H), 1.64 (m, 2H), 1.91 (m, 2H), 2.06 (m, 3H), 2.33 (d, *J* = 14.5 Hz, 1H), 2.53 (td, *J* = 2.3, 13.2 Hz, 1H), 2.97 (td, *J* = 4.1, 15.0 Hz, 1H), 3.11 (dd, *J* = 3.5, 15.0 Hz, 1H), 3.99 (s, 3H), 4.07 (dd, *J* = 5.3, 15.1 Hz, 1H), 4.49 (m, 1H), 7.21-7.45 (m, 5H); ¹³C NMR (100 MHz, CDCl₃) δ 18.2, 27.1, 28.3, 30.8, 33.4, 38.9, 41.9, 42.7, 48.9, 55.3, 58.8, 125.8, 128.2, 129.5, 143.5, 194.6; IR (neat) 2955, 2918, 2849, 2187, 1578, 1445, 1366, 1238 cm⁻¹; HRMS calcd for C₂₀H₃₀NS (M⁺) 316.2099, found 316.2094.

Thionation of the bridged and the fused amide with Lawesson's reagent



25 ml round bottom flask was charged with amide **1** (0.0200 g, 0.070 mmol, 1.0 equiv) Lawesson's reagent (0.0871 g, 0.21 mmol, 3.0 equiv), and toluene (7.0 mL), and the resulting mixture was heated to reflux for 24 h. After the reaction was cooled to rt, the solvent was removed and the reaction was analyzed by NMR. ^1H NMR indicated 31:6:63 mixture of **1**:**2**:**3**. Note: the use of Lawesson's reagent complicates the purification of the final products; the lactams exhibit similar polarity to the decomposition products of the thionating reagent.



8-*tert*-Butyl-9a-phenylhexahydro-1H-pyrrolo[1,2-a]azepine-5(6H)-thione (**5**).

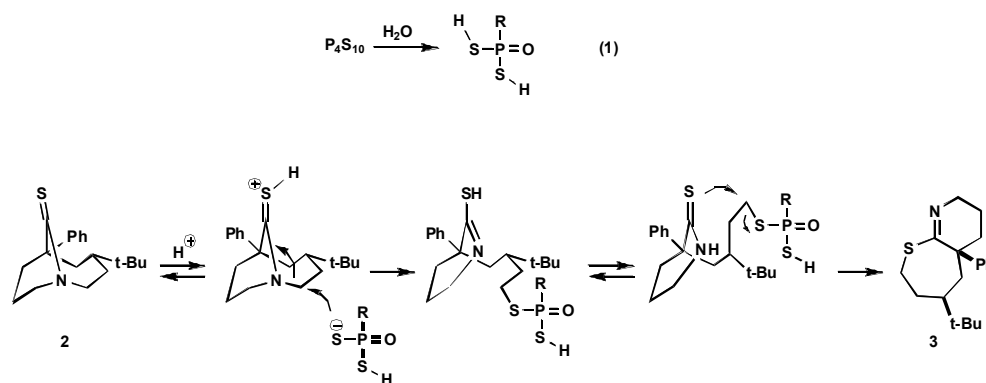
According to the procedure described above, the reaction of amide **4** (0.0500 g, 0.175 mmol, 1.0 equiv), Lawesson's reagent (0.11 g, 0.26 mmol, 1.5 equiv) in toluene (7.0 mL) at reflux for 30 min, afforded after solvent removal and chromatography (1/10-1/4 EtOAc/hexanes), the title compound as white solid (m.p. = 152-3 °C, R_f = 0.73, 1/1 EtOAc/hexanes). Yield 93% (0.0488 g, 0.0162 mmol). ^1H NMR (400 MHz, CDCl_3) δ 0.92 (s, 9H), 1.22-1.38 (m, 2H), 1.43-1.52 (m, 1H), 1.64 (dd, J = 2.8, 10.8 Hz, 1H), 1.73-1.82 (m, 1H), 2.01 (m, 1H), 2.26 (m, 2H), 2.46 (d, J = 13.6 Hz, 1H), 2.60 (td, J = 6.1, 12.8 Hz, 1H), 2.99 (ddd, J = 1.8, 5.0, 12.4 Hz, 1H), 2.87-3.97 (m, 1H), 4.09 (dd, J = 4.8, 9.2 Hz, 1H), 7.12 (d, J = 7.4 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 7.36 (t, J = 7.7 Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 19.8, 26.8, 27.0, 32.6, 39.6, 41.3, 42.7, 44.1, 56.0, 75.4, 124.8, 127.3, 128.7, 145.4, 200.5; IR (neat) 2950, 2916, 2868, 1470, 1443, 1367, 1331, 1252, 1148 cm^{-1} ; HRMS calcd for $\text{C}_{19}\text{H}_{28}\text{NS}$ ($\text{M}^+ + \text{H}$) 302.1942, found 302.1953.

Alternative Mechanism for Rearrangement of **2** to **3**

In an alternative mechanism, phosphonodithioic acid (generated from P_4S_{10} or Lawesson's reagent and traces of moisture, as shown below in equation 1, Scheme A) could protonate bridged thioamide bond. However, as noted by Curphey, phosphorus pentasulfide and its thiophosphates are strong electrophiles² and at present we cannot distinguish between the activation modes of **2**. We also note that reactions with bridged amide **1** were carried out with rigorous exclusion of moisture.

Secondly, it is possible that the electrophilic activation of bridged thioamide **2** occurs at sulfur instead of nitrogen. Although a typical thioamide bond would be expected to undergo protonation at sulfur, in analogy to bridged amides with [4.3.1] ring system which due to the non-planarity of amide bonds are protonated at nitrogen rather than oxygen,^{3,4} we proposed that **2** would also undergo electrophilic attack at nitrogen. We note that there are no examples of bridged thioamides described in literature. Accordingly, the reactivity profile of species analogous to **2** is currently unknown. Study to address the intriguing question of reactivity of bridged thioamides is underway in our laboratories.

Scheme A. Alternative mechanism for rearrangement of a bridged thioamide.



References

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