Pergamon

Tetrahedron Letters 40 (1999) 3363–3366

TETRAHEDRON LETTERS

Newly Intramolecular α-Amidoalkylation Cyclisation: Use of the *N*-Acyliminium Ion with a Sulfur Atom as a Nucleophile.

Nicolas Hucher, Adam Daïch,* Pierre Netchitaïlo, Bernard Decroix

Laboratoire de Chimie, Faculté des Sciences et Techniques de l'Université du Havre, 25 rue Philippe Lebon, BP 540, 76058 Le Havre, France.

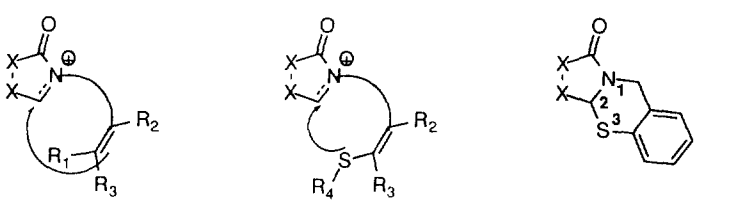
Received 9 February 1999; accepted 2 March 1999

Abstract:

Pyrrolidino(or isoindolo)[1,3]benzothiazines **1a,b** were efficiently synthesized in a four-step sequence from the known *o*-(benzylthio) benzyl alcohol **2**. The key step was the nucleophilic attack of the sulfur atom onto *N*-acyliminium ion **6** which was generated in high acidic medium from ω-carbinol lactam **5**. The last was regioselectively obtained by reduction of the parent imide **4**.
© 1999 Elsevier Science Ltd. All rights reserved.

Keywords: N-Imides-Benzothiazines-π-Cyclisations-Thioethers.

The use of endocyclic *N*-acyliminium ion (type A) in intramolecular α-amidoalkylation cyclisations with various internal nucleophiles has been largely established [1-4]. This process constitutes a versatile methodology to obtain many diverse natural alkaloid products containing either a pyrrolizidine, an indolizidine or a quinolizidine moiety [1,2].



Scheme 1

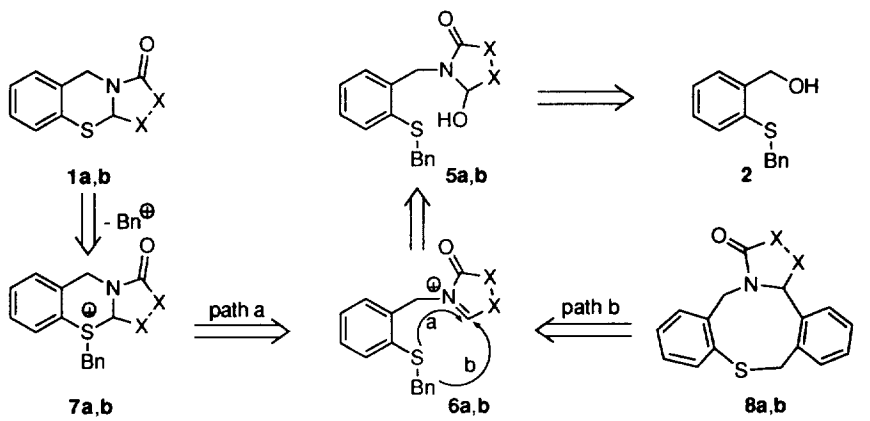
* fax: (+33) 02-35-19-67-71, phone: (+33) 02-35-19-67-54.

0040-4039/99/$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0040-4039(99)00484-0

Although the π-aromatics, olefins, diolefins, alkynes, allyls, homo-allyls, allylsilanes, active methylenes (type A) have been well explored for the carbon-carbon bond construction in organic synthesis [1,2], the intrinsic nucleophilicity of a sulfur atom as an internal nucleophile (type B) to our knowledge has not been yet reported in the literature (Scheme 1).

In view of our interest in the formation-cleavage [5-8] of the thioether linkage in *N,S*-fused heterocyclic systems, we wish now to report our preliminary results obtained in the synthesis of pyrrolo[1,3]benzothiazine **1a** (X-X=CH_2-CH_2) and isoindolo[1,3]benzothiazine **1b** (X-X= benzene) (Scheme 1).

As depicted in Scheme 2, our strategy involved the synthesis of ω-carbinol lactams **5a** and **5b** from the known *o*-(benzylthio)benzyl alcohol **2** [9].

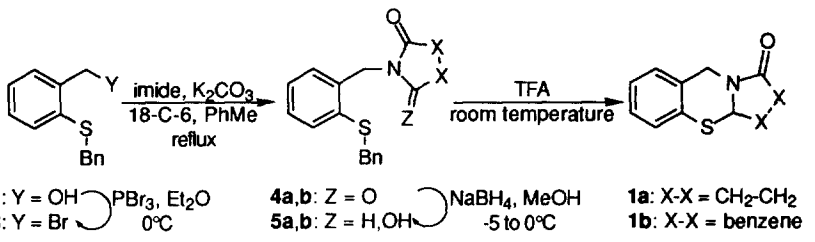


Scheme 2 Retrosynthetic sequence of reaction leading to the cyclised products **1a,b**.

Indeed, taking into account that ω-carbinol lactams **5a** or **5b** could generate the *N*-acyl-iminium ions **6a** or **6b** in an acidic medium [3,4], the ring closure into **1a** or **1b** could take place through an intramolecular α-heteroamidoalkylation cyclisation. The sulfur atom could act as an internal nucleophile in intermediates **6a** or **6b** (Scheme 2, path a), followed by the loss of a stable benzylic cation from the sulfonium ions **7a** or **7b**. The stability of the benzylic carbocation resulting from cleavage of the thioether bond in acidic medium, allied to the high nucleophilicity of the sulfur atom would favour the cyclisation process.

Thus, according to the sequential method illustrated in Scheme 3, bromination of the known alcohol **2** was easily accomplished with phosphorus tribromide (1 equiv) in dry diethyl ether at 0°C for 1.25 h giving the bromide derivative **3** (mp = 54-56°C) in high yield (95%). The chloro analog of compound **3** [9], was also prepared, but the *N*-alkylation process could not be optimized whatever the experimental conditions. Exposure of the bromide **3** to succinimide or phthalimide under solid-liquid phase transfer catalysis (PTC) conditions [8,10], using anhydrous potassium carbonate as a base, and a mixture of potassium

iodide and crown ether 18-C-6 as catalysts gave the *N*-alkylated products **4a** or **4b**. These products were isolated as crystalline solids in 85% (mp = 113°C) and 90% (mp = 134°C) yields respectively. The same products could also be prepared in one step in 51 and 63% yields by condensation of succinimide (or phthalimide) with alcohol **2** in dry THF in the presence of triphenylphosphine and diethyl azidocarboxylate according to the Mitsunobu reaction [11,12].



Scheme 3

Reduction of adduct **4a** was performed with sodium borohydride in dry MeOH with portionwise addition of ethanolic hydrogen chloride [10,13,14], and afforded the hydroxylactam **5a** (mp = 108°C) in 87% yield. In contrary, imide **4b** was converted into corresponding hydroxylactam **5b** (mp = 122°C) in 95% yield without addition of acid but with the use of THF as co-solvent [13].

As expected, the cyclisation of the ω-carbinol lactam **5a** proceeded with high regioselectivity *via* the *N*-acyliminium ion **6a** and the intermediate **7a** to afford 67% of the pyrrolidino[1,3]benzothiazine **1a** [15]. We next examined the effect of an aromatic imide in the cyclisation step from the *N*-acyliminium ion precursor **6b**. Under similar conditions, the ω-carbinol lactam **5b**, gave the cyclised product **1b** in good yield (85%) [15].

Structure assignments of products **1a** and **1b** are based on spectroscopic data. In the ^{1}H-nmr spectra the methylene protons (CH_2-N) appear as an AB system due to the diastereotopic effect with a coupling constant of about 16 Hz characteristic of *gem* protons [14]. Furthermore, these spectra revealed an important deshielding of the angular proton due to the proximity of the sulfur atom compared to the same one in the parent ω-carbinol lactams precursors **5a** ($\Delta\delta$=+0.81 ppm) and **5b** ($\Delta\delta$=+0.80 ppm) respectively. Likewise, the ^{13}C-nmr spectra of products **1a** and **1b** reveal respectively only six and twelve signals in the aromatic region, compared to the parent ω-carbinol lactams **5a** and **5b**. This proves that the intramolecular α-heteroamidoalkylation cyclisation is followed by the loss of the stable benzylic cation. These data, together with elemental analysis and the GC-MS coupling (molecular ions at m/z 205 (for **1a**) and 253 (for **1b**)), clearly establish the structure for **1a**

and **1b** as 5a,6,7,10-tetrahydropyrrolo[2,1-b][1,3]benzothiazin-8-one and 5a,12-dihydro-isoindolo[1,2-b][1,3]benzothiazin-10-one respectively.

In summary, we have described a straightforward synthesis of pyrrolo[1,3]benzothiazine **1a** and isoindolo[1,3]benzothiazine **1b** in four steps from *o*-(benzylthio)benzyl alcohol **2**. The ω-carbinol lactams were obtained easily, and under acidic treatment, they furnished the cyclised lactams **1a,b** through the intramolecular sulfuration of the intermediate *N*-acyliminium ion and debenzylation. Applications of this strategy to the synthesis of new fused *N,S*-heterocyclic systems are in progress and the results will be reported in due course.

Achnowledgments.

The authors wish to thank Région de Haute Normandie, France, for financial support for this work (Regional Scholarship:1996-1999).

References

* This work was presented, in part, at the XVIII[th] European Colloquium on Heterocyclic Chemistry (ECHC 98), Rouen, October 4th-7th, 1998, France.

[1] Speckamp WN. Rec. Trav. Chim. Pays-Bas. 1981; 100: 345-354.

[2] Speckamp WN, Hiemstra H. Tetrahedron. 1985; 41: 4367-4416.

[3] Hiemstra H, Speckamp WN. In the alkaloids. Brossi A. New York: Eds Academic Press, 1988; 32: 271-339.

[4] Hiemstra H, Speckamp WN. In Comprehensive Organic Synthesis. Trost BM, Fleming I. Oxford: Eds Pergamon press, 1991; 2: 1047-1082.

[5] Jilale A, Decroix B, Morel J. Chemica Scripta. 1987; 27: 423-428.

[6] Daich A, Decroix B. J. Heterocyclic Chem. 1991; 28: 1881-1884.

[7] Pigeon P, Decroix B. Synthetic Commun. 1997; 27: 1423-1431.

[8] Mamouni A, Daich A, Decroix B. Synthetic Commun. 1997; 27: 2241-2249.

[9] Stacy GW, Villaescusa FW, Wollner TE. J. Org. Chem. 1965; 30: 4074-4078.

[10] Mamouni A, Daich A, Decroix B. J. Heterocyclic Chem. 1996, 33: 1251-1258.

[11] Mitsunobu O, Wada M, Sano T. J. Am. Chem. Soc. 1972; 94: 679-691.

[12] Mitsunobu O. Synthesis. 1981; 1-28.

[13] Ishihara Y, Kiyota Y, Goto J. Chem. Pharm. Bull. 1990; 38: 3024-3030.

[14] Wijnberg JBPA, Schoemaker HE, Speckamp WN. Tetrahedron. 1978; 34: 179-187.

[15] All compounds, including intermediates **3**, **4a,b** and **5a,b**, gave satisfactory physicochemical data. A representative procedure is as follows: To a stirred solution of hydoxylactam **5a** or **5b** (6 mmol) was added trifluoroacetic acid (10 ml). After 24 hours of reaction at room temperature, the reaction mixture was diluted with water (50 ml) and neutralised with 10% aqueous sodium hydroxide. The organic layer was separated, washed with water (50 ml), dried and concentrated *in vacuo*. The resulting crude white solid was purified by flash chromatography on a silica gel column eluting with dichloromethane/hexane (9/1) followed by recrystallization from anhydrous alcohol and gave the expected tricyclic products **1a** or **1b**.

Selected data for product **1a**: mp=68°C (decomposition); ^{1}H nmr (200.13 MHz, $CDCl_3$): δ 1.85-2.05 (m, 1H, 1H-pyrrolidinone), 2.35-2.70 (m, 3H, 3H-pyrrolidinone), 4.23 (d, 1H, J=17 Hz, CH_2-N), 4.85-4.90 (m, 1H, 1H-pyrrolidinone), 5.04 (d, 1H, J=17 Hz, CH_2-N), 7.06-7.20 (m, 4H, 4H-aromatic); ms: (EI) m/z 205 (M^+); *Anal.* Calcd. for $C_{11}H_{11}NOS$ (205.27): C, 64.36; H, 5.40; N, 6.82. Found: C, 64.13; H, 5.12; N, 6.69.

Selected data for product **1b**: mp=159°C; ^{1}H nmr (200.13 MHz, $CDCl_3$): δ 4.62 (d, 1H, J=17.5 Hz, CH_2-N), 5.31 (d, 1H, J=17.5 Hz, CH_2-N), 5.80 (s, 1H, CH), 7.16-7.26 (m, 4H, 4H-aromatic), 7.50-7.64 (m, 2H, 2H-aromatic), 7.77-7.96 (m, 2H, 2H-aromatic); ms: (EI) m/z 253 (M^+); *Anal.* Calcd. for $C_{15}H_{11}NOS$ (253.31): C, 71.12; H, 4.38; N, 5.53. Found: C, 71.05; H, 4.29; N, 5.48.