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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.

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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. \otimes 1999 Elsevier Science Ltd. All rights reserved.

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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].



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

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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=CH2-CH2) 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].



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-acyliminium 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].



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 hydroxy-lactam 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 ¹Hnmr spectra the methylene protons (CH₂-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 ¹³Cnmr 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-dihydroisoindolo[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.

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- [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); ¹H nmr (200.13 MHz, CDCl₃): δ 1.85-2.05 (m, 1H, 1H-pyrrolidinone), 2.35-2.70 (m, 3H, 3H-pyrrolidinone), 4.23 (d, 1H, J=17 Hz, CH₂-N), 4.85-4.90 (m, 1H, 1H-pyrrolidinone),

5.04 (d, 1H, J=17 Hz, CH₂-N), 7.06-7.20 (m, 4H, 4H-aromatic); ms: (EI) m/z 205 (M⁺); *Anal.* Calcd. for C₁₁H₁₁NOS (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; ¹H nmr (200.13 MHz, CDCl₃): δ 4.62 (d, 1H, J=17.5 Hz, CH₂-N), 5.31 (d, 1H, J=17.5 Hz, CH₂-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 C₁₅H₁₁NOS (253.31): C, 71.12; H, 4.38; N, 5.53. Found: C, 71.05; H, 4.29; N, 5.48.