A new access to isoindolo[2,1-b][2,4]benzodiazepines through an N-acyliminium ion amide cyclization

Pascal Pigeon, Bernard Decroix

► To cite this version:

Pascal Pigeon, Bernard Decroix. A new access to isoindolo[2,1-b][2,4]benzodiazepines through an N-acyliminium ion amide cyclization. *Tetrahedron Letters*, 1997, 38 (17), pp.2985-2988. 10.1016/S0040-4039(97)00539-X . hal-01230422

HAL Id: hal-01230422

<https://hal.science/hal-01230422>

Submitted on 11 Feb 2018

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

A New Access to Isoindolo[2,1-b][2,4]benzodiazepines through an *N*-Acyliminium Ion - Amide Cyclization

Pascal Pigeon and Bernard Decroix*

Laboratoire de Chimie, Faculté des Sciences et des Techniques de l'Université du Havre, 30, rue Gabriel Péri, 76600 Le Havre, France

Abstract: Isoindolo[2,1-b][2,4]benzodiazepines **11a-c** were synthesized from hydroxylactam-acid **5** when it was treated successively with thionyl chloride, ammonia (or an alkylamine) and *p*-toluenesulfonic acid.

Because of their potential biological properties many synthetic efforts have been devoted in the recent years to the preparation of [1,4] or [1,3] benzodiazepines annelated to different rings as pyrrole or pyrrolidine^{1,2}. Since the isomeric [2,4]benzodiazepines are unknown or almost unknown in the literature, we have been interested in their syntheses and recently we reported the Beckmann³⁻⁵ or Schmidt^{4,5} rearrangements of ketones leading to [2,4]thienodiazepines analogous to [2,4]benzodiazepines. Derivatives related to **11** have been synthesized according to different pathways⁶⁻⁹ and now we wish to report a new approach to isoindolo[2,4]benzodiazepines **11** through an intramolecular cyclization of an *N*-acyliminium ion with an amide function. It has been demonstrated¹⁰ that an *N*-acyliminium ion could react with a tertiary amine to give a quaternary aminoalkylamide salt or a biscarbamate when reacted with a carbamate. Based on this work, we tried a reaction with acetamide¹¹ and we obtained the expected bisamides **2** from hydroxylactams **1** (Scheme 1) in a quantitative yield.

Scheme 1

Thus, we hoped to realize a similar reaction from **9** during an intramolecular cyclization reaction procedure. Since the required hydroxylactam-amides **9a-c** could not be obtained directly from ester **3**, because the amine (butylamine, methylamine) opened the imide function, or from ester **4**, which did not react when treated with ammonia or amine, we investigated another approach leading to **11** (Scheme 2). In a similar manner to our reported work¹² reaction of the potassium salt of phthalimide with methyl *o*-bromomethyl-benzoate furnished the phthalimide derivative **3** (56%). Reduction of **3** with sodium borohydride gave the hydroxylactam-ester **4** and saponification of which led to the corresponding hydroxylactam-acid **5**. Reaction of **5** with thionyl chloride followed by a treatment with ammonia (gas) gave the aminolactam-amide **10a** (47%) and a mixture of inseparable compounds containing the diazepine **11a** (trace). This reaction occurred *via* the chlorolactam-acid chloride intermediate **6**. A similar reaction conducted with a concentrated ammonia solution provided a mixture of the three compounds **9a**, **11a** (minor products) and **10a** (major product). Compound **10a** (35%) could be easily separated from this mixture using an acidic extraction with hydrochloric acid solution. Since α -chlorolactams are very susceptible to hydrolysis¹⁰ compound **9a** would result from a hydrolysis of the chlorolactam **6** leading to the intermediate **7** followed by the reaction of ammonia. Furthermore, if traces of starting acid **5** were detected, the possible oxazepine **8** has never been observed. Since, in our conditions, the acyl chloride function seem less reactive than the chlorolactam towards water and to minimize the quantity of **10a**, we treated **6a**¹³ first with water during 10 minutes at room temperature followed by the addition of a concentrated ammonia solution. In this manner four compounds were formed. The recovered starting acid **5** (13%) was separated from the mixture by a selective extraction (NaOH) and it could be used for a next reaction. Then the aminolactam-amide **10a** (15%) was separated as described above and the resulting mixture of **9a** and **11a** was treated with *p*-toluenesulfonic acid to give the expected [2,4]benzodiazepine **11a** (60% calculated from **5**)¹⁴. Actually, as mentioned for the above transformation **1** $\rightarrow$ **2**, under the acidic medium the hydroxylactam **9a** generated an *N*-acyliminium ion which reacted (two days) with the amide function to give the cyclized product **11a**.

A generalization of this methodology was accomplished by using alkylamines (methylamine, butylamine). The corresponding *N*-alkyl derivatives **11b** (R=Me, 60%)¹⁵ and **11c** (R=Bu, 72%)¹⁶ were obtained accompanied by a small amount of acid **5** (<10%), nevertheless no trace of **10b** or **10c** could be detected.

In summary, we report a short synthesis of isoindolo[2,1-b][2,4]benzodiazepines via an intramolecular cyclization of an *N*-acyliminium ion with an amide. Further studies to generalize this reaction (case of aromatic amines and cases of aromatic or heteroaromatic rings in the place of benzene ring) are now in progress.

Scheme 2

REFERENCES AND NOTES

1. Thurston, D.E.; « Advances in the study of pyrrolo[2,1-c][1,4]benzodiazepine Antitumor Antibiotics » in « Molecular aspects of anticancer drug - DNA interactions », Neidle, S; Waring, M.J. Eds. The Macmillan Press Ltd., 1993, vol 1, pp. 54-88.
2. Kamel, A.; Reddy, B.S.P.; Reddy, B.S.N. *Tetrahedron Lett.*, **1996**, 37, 6803-6806.
3. Marchalin, S.; Decroix, B. *J. Heterocyclic Chem.*, **1993**, 30, 667-670.
4. Lebosquain, D.; Decroix, B. *Heterocycles*, **1993**, 36, 2303-2314.
5. Marchalin, S.; Decroix, B. *J. Heterocyclic Chem.*, **1994**, 31, 495-499.
6. Hatt, H.N.; Stephenson, E.F.M. *J. Chem. Soc.*, **1952**, 199-205.
7. Stephenson, E.F.M. *J. Chem. Soc.*, **1952**, 5024-5027.
8. Eguchi, S.; Takeuchi, H. *J. Chem. Soc., Chem. Commun.*, **1989**, 602-603.
9. Lessel, J. *Pharmazie*, **1993**, 48, 812-816.
10. Speckamp, W.N.; Hiemstra, H., *Tetrahedron*, **1985**, 41, 4367-4416.
11. Pigeon, P. Ph.D. Dissertation, University of Le Havre, **1996**.
12. Pigeon, P.; Decroix, B. *Bull. Soc. Chim. Fr.*, **1997**, in press.
13. The hydroxylactam-acid **5** (2.83 g, 10 mmol) and thionyl chloride (2 ml, 27 mmol) were refluxed in dry dichloromethane during one hour. The solution was cooled, then water (approx. 5 ml) was added. After strong stirring for 10 minutes, concentrated ammonia (approx. 20 ml for **11a**) or 30% aqueous methylamine (approx. 20 ml for **11b**) or pure butylamine (1 ml for **11c**) was added. The mixture was stirred for 30 minutes then was poured in 10% aqueous sodium hydroxide. The organic layer was washed successively with 10% hydrochloric acid, saturated sodium hydrogen carbonate, water then was dried and concentrated. The residue was heated in toluene to reflux (Dean-Stark apparatus) with a catalytic amount of *p*-toluenesulfonic acid for two days. After cooling, the solution was washed with saturated sodium hydrogen carbonate then with water and was dried and concentrated. Recrystallization of the solid (chloroform for **11a**, ethanol for **11b,c**) furnished the corresponding diazepines.
14. Physical data for **11a**: yield 60%; mp >260°C (decomposition); IR: 3182 (NH), 1718 (C=O), 1653 (C=O) cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 4.55 (d, 1H, H₅, J = 14 Hz), 5.04 (d, 1H, H₅, J = 14 Hz), 5.73 (d, 1H, H_{11b}, J = 6 Hz), 6.65 (d, 1H, NH, J = 6 Hz), 7.04-7.64 (m, 6H, H_{arom}), 7.82-7.94 (m, 2H, H₁₊₈); ¹³C NMR: δ 44.1 (CH₂), 66.2 (CH), 122.6 (CH), 124.5 (CH), 128.7 (CH), 129.5 (2CH), 129.8 (CH), 131.9 (2CH), 132.4 (C), 132.9 (C), 135.9 (C), 140.1 (C), 165.1 (CO), 170.6 (CO).
15. Physical data for **11b**: yield 60%; mp 221°C; IR: 1695 (C=O), 1651 (C=O) cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 2.81 (s, 3H, CH₃), 4.37 (d, 1H, H₅, J = 14 Hz), 5.02 (d, 1H, H₅, J = 14

Hz), 5.87 (s, 1H, H_{11b}), 7.28-7.36 (m, 1H, H_{arom}), 7.40-7.65 (m, 5H, H_{arom}), 7.79-7.92 (m, 2H, H₁₊₈); ¹³C NMR: δ 30.1 (CH₃), 44.1 (CH₂), 70.9 (CH), 124.1 (CH), 124.2 (CH), 129.0 (CH), 129.1 (CH), 129.8 (CH), 130.2 (CH), 131.9 (CH), 132.0 (C), 132.1 (CH), 133.8 (C), 135.9 (C), 137.9 (C), 165.2 (CO), 171.4 (CO).

16. Physical data for **11c**: yield 72%; mp 174°C; IR: 1692 (C=O), 1639 (C=O) cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 0.61 (t, 3H, CH₃, J = 7 Hz), 0.88-1.47 (m, 4H, CH₂-CH₂), 2.86-3.06 (m, 1H, NCH₂), 3.73-3.93 (m, 1H, NCH₂), 4.36 (d, 1H, H₅, J = 14 Hz), 5.00 (d, 1H, H₅, J = 14 Hz), 5.85 (s, 1H, H_{11b}), 7.26-7.35 (m, 1H, H_{arom}), 7.38-7.50 (m, 3H, H_{arom}), 7.50-7.60 (m, 2H, H_{arom}), 7.74-7.88 (m, 2H, H₁₊₈); ¹³C NMR: δ 13.2 (CH₃), 19.9 (CH₂), 31.3 (CH₂), 43.2 (CH₂), 44.0 (CH₂), 71.0 (CH), 124.0 (CH), 124.4 (CH), 128.8 (CH), 129.0 (CH), 129.6 (CH), 130.1 (CH), 131.6 (CH), 131.8 (CH+C), 134.0 (C), 136.1 (C), 137.6 (C), 164.7 (CO), 170.9 (CO).