Tetrahedron Letters 56 (2015) 1153–1158

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Lewis-acid catalyzed *N*-acyliminium ion cyclodimerization: synthesis of symmetrical 1,4-dioxanes

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ARTICLE INFO

Article history:
Received 19 December 2014
Revised 6 January 2015
Accepted 7 January 2015
Available online 17 January 2015

Keywords:
Amines
N-Acyliminium
Acid catalysis
Cyclodimerization
1,4-Dioxane

ABSTRACT

The cyclodimerization reaction of *N*-substituted-5-hydroxy-pyrrolydinones promoted by $BF_3{\cdot}Et_2O$ and HCl to obtain symmetrical 1,4-dioxane derivatives was achieved in moderate to good yields, mild conditions, and short reaction times. These transformations render a promising alternative route that provides access to diverse 1,4-dioxane derivatives with a wide structural diversity.

Introduction

The synthesis of heterocycles is a very important area in organic chemistry because of their strong presence in natural products and pharmaceutical drugs.[1]

Heterocyclic compounds, especially containing carbon-nitrogen and carbon-oxygen bonds, have great importance, and researchers are constantly searching for new approaches to synthesize these molecules. Nitrogen-containing heterocyclic compounds, especially succinimide derivatives, are important intermediates in synthesis and key structures in biologically active products.[2,3] Succinimide derivatives are converted to chiral pyrrolidine motifs, which display activity in many biological systems, by simple transformations.[4]

N-Acyliminium ions play an important role in organic synthesis[5] since they are reactive intermediates involved in the synthesis of many compounds with interesting biological properties. Nucleophilic addition to *N*-acyliminium ions is an important method to provide α-functionalized amino compounds such as nitrogen heterocycles.[6] Of particular interest are the intermolecular nucleophilic substitution reactions of cyclic *N*-acyliminium ion precursors (*N*,*O*-acetal derivatives) with carbon-based nucleophiles through activation by a Lewis acid.

The reactivity affords exceptionally useful methodologies for carbon–carbon bond and carbon-heteroatom bond formation, both in intermolecular and intramolecular processes.[3] These species have been generated from amides or lactams, which bear a good leaving group at the α-position nitrogen atom in acidic media.

The *N*-acyliminium ion is a key intermediate for the addition of different nucleophiles including allylsilanes, alkyl-, aryl-, allyl-, alkynylmetal, isonitriles, enol derivatives, TMSCN, and aromatics.[5]

1,4-Dioxanes derivatives are important biologically active compounds.[7] Due to the importance of 1,4-dioxanes, many approaches for the synthesis of this six-membered heterocyclic compounds have been described. Among the methods are: (a) oxyselenylation of dienes with enantiopure diols;[8,9] (b) Mitsunobu cyclization of diols;[10] (c) photoinduction electron transfer cyclization of an appropriate diene;[11] (d) condensation of glyoxalic acid with chiral hydrobenzoin,[12] (e) intramolecular ring opening of oxirane by an alcohol moiety;[13] and (f) cyclodimerization of epoxide,[14] phosphoric acid-catalyzed desymmetrization of cyclohexadienones.[15]

Among the many applications[14] of 1,4-dioxane derivatives, we can mention some examples of drugs containing a 1,4-dioxane ring: doxazosin (Cardura) used to treat the symptoms of an enlarged prostate (benign prostatic hyperplasia or BPH) to treat

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http://dx.doi.org/10.1016/j.tetlet.2015.01.059
0040-4039/

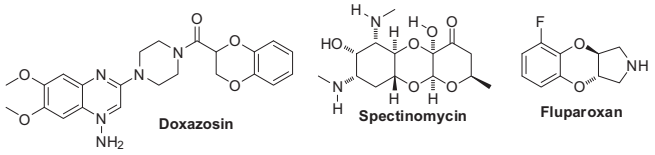


Figure 1. Structure of drugs containing 1,4-dioxane ring.

high blood pressure;[16] spectinomycin (Trobicin) is a useful antibiotic for the treatment of bacterial infection and gonorrhea,[17] and fluparoxan (GR-50,360) is a potent and highly selective α_2-adrenergic receptor antagonist which is being investigated as an antidepressant[18] (Fig. 1).

Results and discussion

We report here a direct method for the synthesis of heterocyclic 1,4-dioxane derivatives via acid-catalyzed cyclodimerization reactions of cyclic *N*-acyliminium ions. This opportunity should be taken to mention that Pyne and co-workers[19] published an example of this approach in a study on the synthesis of stemocurtisine employing acyliminium ions, but did not perform a systematic study.

In continuation of our interest in the chemistry of acyliminium ions,[20–24] we developed the synthesis of 1,4-dioxanes via dimerization reactions of *N*-substituted acyliminium ions.

We began the synthesis of our starting material using L-malic acid, which is a precursor of the *N*-acyliminium ion[1,25] reaction leading to pyrrolidin-2-one derivative **3**.

Acid **1** was successively treated with acetyl chloride, primary amines, and again with acetyl chloride to afford imide **2**. Regio- and stereoselective reduction of the imide **2** was then achieved by reaction with an excess of sodium borohydride in ethanol/THF at −30 °C for 30 min to afford the 5-hydroxy-2-pyrrolidin-2-one **3** as a mixture of *cis*/*trans* diastereoisomers (see Table 1).

Fourteen imides (**2**) were synthesized containing primary aromatic, alkyl-, acetyl-, benzyl-, propargyl-, and triazolyl-amines, all in moderate to high yields (Table 1, entries 1–14).

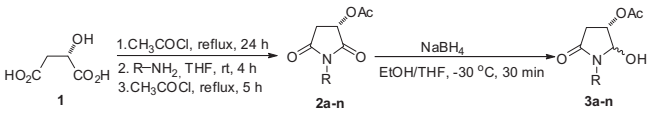
The presence of electron-donating or electron-withdrawing groups at the aromatic rings does not appear to interfere with the performance of the reaction leading to moderate yields; also, the occupied position in the ring does not seem to affect yields in both reactions. Alkynyl groups such as propargyl (Table 1, entries 12–14) also gave moderate yields. These last compounds were obtained via click chemistry reaction. The acyl group (Table 1, entry 8) afforded the product in 56% yield.

The stereochemistry of the newly created chiral center in the products was assigned by ^{1}H NMR analysis of the crude reaction mixtures. The *cis* relative stereochemistry of the major product was established by an analysis of the multiplicity and vicinal coupling constants of the hydrogen attached to the carbon that underwent nucleophilic attack (H-5).

In this way, the relative stereochemistry of compounds was assigned by correlation to the chemical shifts and coupling constant data of similar compounds already described in the literature. In addition, the vicinal coupling constant J^3 (H5–H4) for the *syn*-isomer always has a smaller value than the *trans*-isomer. In addition, the H5 of the *cis*-isomer appears up-field of the anti-isomer. These chemical correlations are in full agreement with the major isomer obtained here; thus, the relative stereochemistry of the major isomer was assigned as *cis*.[26]

Following production of the *N*-substituted-5-hydroxy-pyrrolidinone, we began surveying the best reaction conditions to obtain the cyclodimer of the acyliminium ion, reacting

Table 1
Synthesis of imides and 5-hydroxy-4-acetoxypyrrolydones



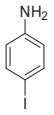
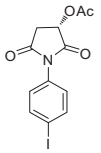
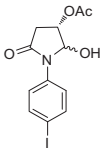
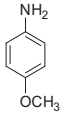
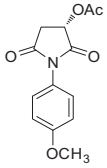
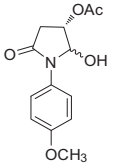
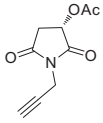
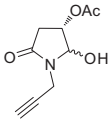
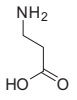
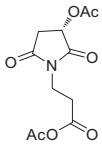
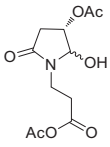
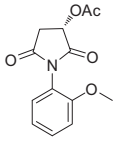
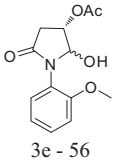
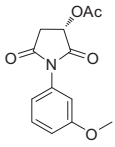
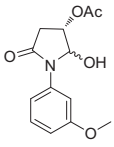
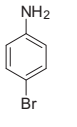
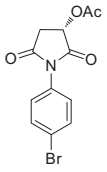
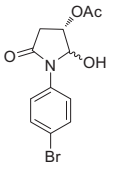
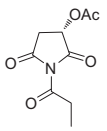
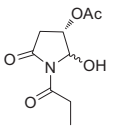
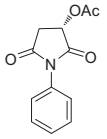
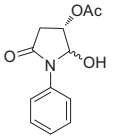
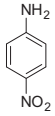
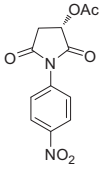
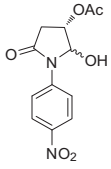
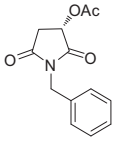
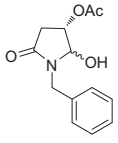
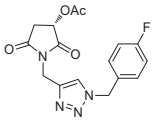
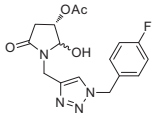
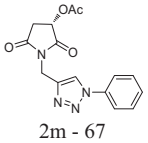
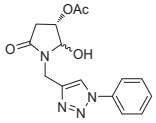
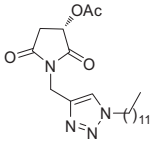
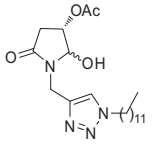
Entry	Amine	Product/yield (%)	Product/yield (%)	Ratio *cis*/*trans*
1		 2a - 70	 3a - 65	80:20
2		 2b - 76	 3b - 66	70:30
3		 2c - 73	 3c - 62	80:20
4		 2d - 65	 3d - 50	85:15
5		 2e -58	 3e - 56	90:10
6		 2f - 70	 3f - 58	75:25
7		 2g - 76	 3g - 65	75:25
8		 2h - 66	 3h - 56	80:20
9		 2i - 79	 3i - 69	90:10

Table 1 (*continued*)

Entry	Amine	Product/yield (%)	Product/yield (%)	Ratio *cis/trans*
10		 2j - 75	 3j - 66	60:40
11		 2k - 78	 3k - 83	65:35
12		 2l - 70	 3l - 60	70:30
13		 2m - 67	 3n - 58	65:35
14		 2n - 70	 3n - 56	70:30

5-hydroxy-pyrrolydinone with ethyl triptophane, trying to obtain the pyrrolidone amino esters. To our surprise, the only product obtained was the 1,4-dioxane dimer **4g**. In view of that interesting result, various reaction conditions were surveyed using Lewis acids in different stoichiometries, bases or acids, and solvents to achieve the cyclodimer.

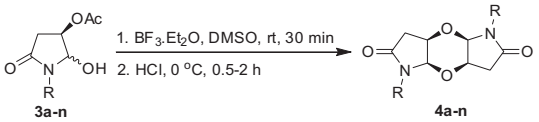
The Lewis acid that afforded the best yield (88%) of the cyclodimer **4g** was $BF_3{\cdot}Et_2O$. However, in the presence of a protic solvent like methanol, no product was detected. The same was observed when the reaction was carried out in THF and PMDTA (*N*,*N*,*N*′,*N*′,*N*″-pentamethyldiethylenetriamine) as a base. Also, with $POCl_3$ as a catalyst, the reaction did not afford the dimer. The reactions with bases such Et_3N, Py, DMAP, and PMDTA in the presence of $BF_3{\cdot}Et_2O$ produced low to moderate yields ranging from 20% to 52%.

In the absence of a base, the reaction proceeded, leading to yields from low (20%) to good (80%). Acids such as CF_3CO_2H and HCl gave almost the same high yields, 83% to 88%. Reaction in the presence of tryptophan ester led to good yields of the product (80%), however its absence led only to traces (in GC–MS) of the product, in both cases using $BF_3{\cdot}Et_2O$. Using HCl without tryptophan ester and $BF_3{\cdot}Et_2O$, the product was achieved in 40%. These last two reactions were carried out in DMSO as a solvent for 18 h. The use of a glycine ester afforded the same results.

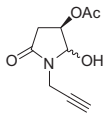
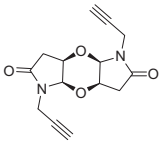
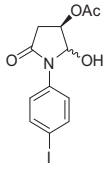
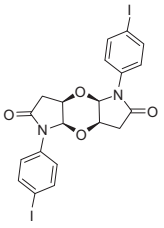
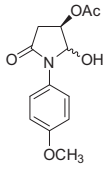
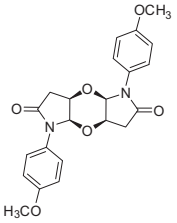
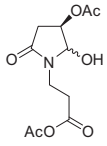
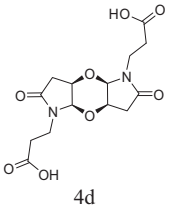
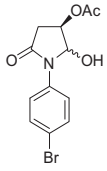
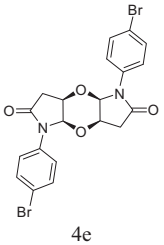
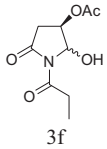
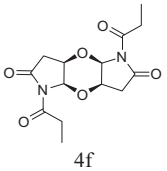
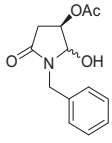
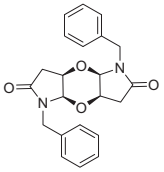
With the optimal reaction conditions determined, we next explored the substrate scope of 5-hydroxy-4-acetoxypyrrolidone for dimerization (Table 2).

As shown in Table 2, all starting materials exhibited good reactivity, leading to 1,4-dioxane derivatives in yields ranging from

Table 2
Lewis Acid cyclodimerization of *N*-substituted-5-hydroxy-4-acetoxypyrrolidone



3a-n 4a-n

Entry	Pyrrolidone	Product	Yield (%)
1	 3a	 4a	71
2	 3b	 4b	60
3	 3c	 4c	62
4	 3d	 4d	58
5	 3e	 4e	70
6	 3f	 4f	59
7	 3g	 4g	88

(*continued on next page*)

Table 2 (*continued*)

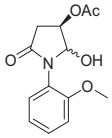
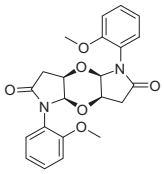
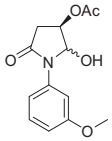
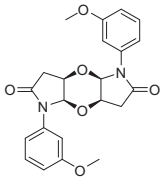
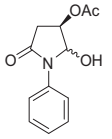
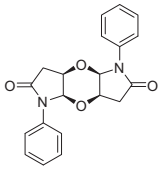
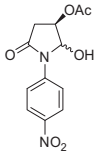
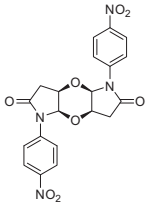
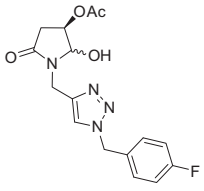
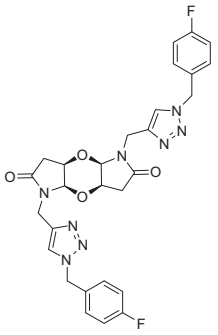
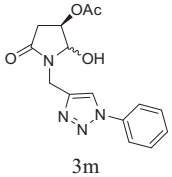
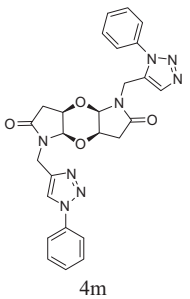
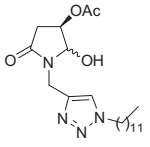
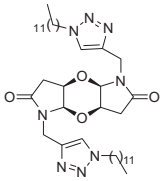
Entry	Pyrrolidone	Product	Yield (%)
8	 3h	 4h	66
9	 3i	 4i	70
10	 3j	 4j	80
11	 3k	 4k	55
12	 3l	 4l	56
13	 3m	 4m	55

Table 2 (*continued*)

Entry	Pyrrolidone	Product	Yield (%)
14	 3n	 4n	60

Reaction conditions: **3g** (0.249 g, 1.0 mmol, 1.0 equiv) in DMSO (5 mL) at 25 °C under N_2 atmosphere was added $BF_3{\cdot}Et_2O$ (4.0 equiv) dropwise. The reaction mixture was stirred at room temperature for 30 min. Then HCl (1.5 equiv) was added drop by drop for 5 min and left for 1 h.

55% to 88% (Table 2, entries 1–14). *N*-Aryl substituted pyrrolidones with electron-withdrawing groups in the benzene ring (such as 4-I, 4-Br, and 4-NO_2) provided products in moderate yields (see Table 2, entries **4b**, **4e**, **4k**, 60%, 70%, and 55%, respectively). Electron-donating groups such as MeO-, regardless of the position (*o*, *m* or *p*) on the ring, showed no significant electronic effects and afforded the desired 1,4-dioxane derivatives products **4c** in 62%, **4h** in 66% and **4i** in 70% in very similar yields (Table 2). On the other hand the benzene ring gave a high yield, 80% (Table 2, entry **4j**).

Groups such as alkyl and acetyl provided the corresponding products in moderate yields: **4d** and **4f** in almost the same yields of 58% and 59%, respectively (Table 2). However, when the reaction was carried out with the *N*-benzyl group, the 1,4-dioxane derivative was achieved in 88% yield (Table 2, entry **4g**).

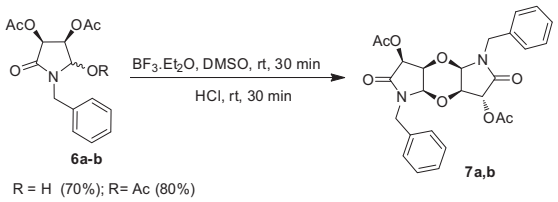
The *N*-propargyl pyrrolidone (**2l**) was converted into a 1,4-dioxane derivative in 71%. The presence of the terminal alkyne at the *N*-propargyl pyrrolidone allowed the preparation via click chemistry of 1,2,3-triazole-1,4-disubstituted and the further conversion of three triazoles into the 1,4-dioxane derivatives in almost the same yields (Table 2, entries **4l**, **4m**, and **4n**), 56%, 55%, and 60%, respectively, with interesting structural architecture. This reaction system tolerated electron-poor and electron-rich substituents at the N-atom in the pyrrolidone ring, leading to 1,4-dioxane derivatives.

A plausible reaction mechanism for the formation of 1,4-dioxane derivative is proposed. The starting material (**a**) is treated with BF_3.etherate, which generates *N*-acyliminium ion (**b**, calcd 232.0968, found 232.0722). The reduction of **b** took place in the presence of catalytic HCl to give intermediate **c** (calcd 189.0863, found, 189.0799 (M−H)). Then intermediate **c** reacts with the intermediate **b** to give intermediate **d** (calcd 420.1758, found, 420.1700 (M−H)), which after reduction cyclizes to form dioxane product (Fig. 3). This information was obtained through HRMS in a negative mode.

Similar reactions with the diacetate *N*-benzyl-3,4-diacetoxypyrrolidone **6a**–**b** afforded the 1,4-dioxane dimer in good yields in both cases, using **7a** with the free hydroxyl group (70%) or in the acetyl form **7b** (80%) (Scheme 1).

Confirmation of the NMR results was accomplished with the X-ray crystal structure of the 1,5-dibenzyloctahydro-[1,4]dioxino[2,3-b:5,6-b′]dipyrrole-2,6-dione **4g** (Fig. 2). Slow recrystallization from ethyl acetate provided suitable crystals for determination of the crystal structure.

Studies aimed at examining the mechanism for the cyclodimerization reactions and the possible biological activities of these novel 1,4-dioxane derivatives are currently being evaluated; further applications of this method to other targets are now underway.



Scheme 1. Cyclodimerization of 3,4-diacetoxypyrrolydone.

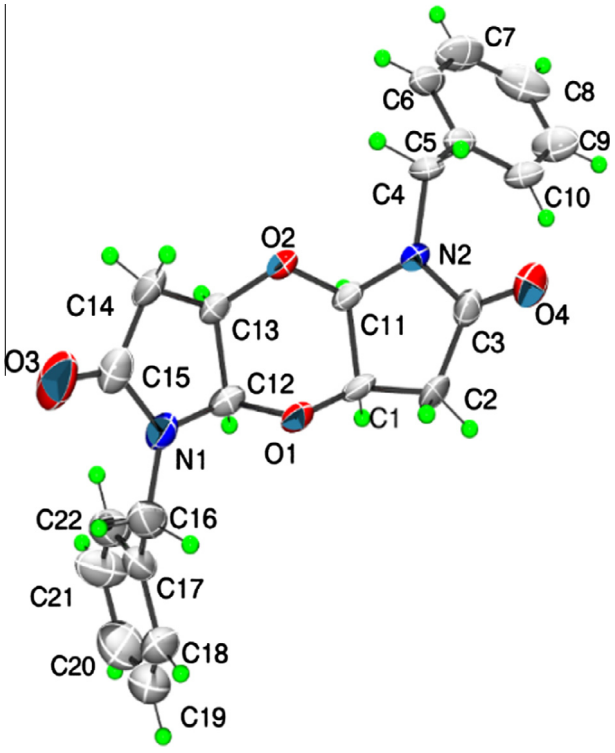


Figure 2. The molecular structure of 1,5-dibenzyloctahydro-[1,4]dioxino[2,3-b:5,6-b′]dipyrrole-2,6-dione (**4g**).

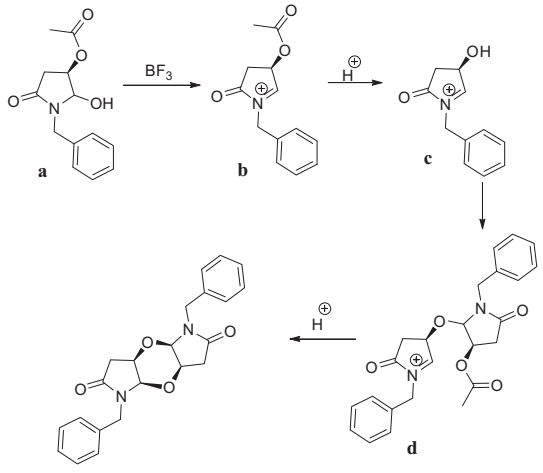


Figure 3. Proposed mechanism for the formation of 1,4-dioxane.

Conclusion

In conclusion, we have presented a simple and mild methodology to synthesize 1,4-dioxane ring derivatives through a dimerization reaction of *N*-substituted-5-hydroxy-2-oxopyrrolidones under acidic conditions employing Lewis acid/HCl in moderate to good yields. These transformations render a promising alternative route that provides access to symmetrical 1,4-dioxane derivatives with a wide structural diversity.

Acknowledgments

The authors are grateful for the financial support provided by FAPESP—São Paulo Research Foundation (Grant 2012/00424-2 and 2011/11499-0 for fellowship to B.A.—2012/17954-4), CNPq—National Council for Scientific and Technological Development (308.320/2010-7 to H.A.S. and 305626/2013-2 to J.Z.-S.) and FINEP (grant 01.09.0278.04, D.C.P.).

Supplementary data

Experimental details and analytical data for all new compounds, including ^{1}H and ^{13}C NMR spectra. CCDC-1031271 (for compound **4g** Table 2) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.01.059.

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