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Acid-mediated intramolecular cationic cyclization using an oxygen atom as internal nucleophile: synthesis of substituted oxazolo-, oxazino- and oxazepinoisoindolinones†,‡

Jana Sikoraiová,[a] Štefan Marchalín,[a] Adam Daïch[b,*] and Bernard Decroix[b]

[a]*Department of Organic Chemistry, Slovak University of Technology, Radlinského 9, Sk-81237 Bratislava, Slovakia*
[b]*Laboratoire de Chimie de l'Université du Havre, Faculté des Sciences & Techniques, URCOM, EA 3221, 25 Rue Philippe Lebon, B.P. 540, F-76058 Le Havre Cedex, France*

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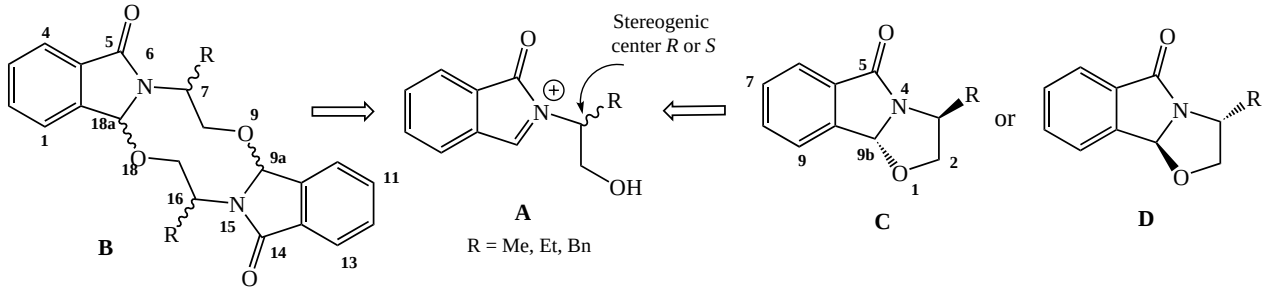
Abstract—Efficient assembly of substituted oxazolo-, oxazino- and oxazepinoisoindolinones (**5**–**7**, **12**–**15** and **19**) is described in three steps according to an acidic α-oxoamidoalkylation reaction from ready available phthalic anhydride by successive imidation, sodium borohydride reduction and intramolecular cationic cyclization involving *N*-acyliminium species. The relative stereochemistry accompanying these reactions was also discussed.

1. Introduction

During the last years, numerous groups, notably this of Meyers,[1] have demonstrated the synthetic utility of the bicyclic *N*,*O*-acetal product as a building block for the construction of a wide variety of natural and unnatural carbocyclic and azacyclic compounds including simple and complex alkaloids.[1] Also, these acetal intermediates commonly known as the bicyclic lactams have been employed in various ways in synthesis of tertiary and quaternary carbon centres at α-position of a nitrogen lactam.[1,2]

Because of the more potential of theses species, valuable efforts continue to be made towards their syntheses and uses. So, known syntheses of these products include: (i) the cyclodehydration process between an amino-alcohol and an ketoacid;[3,4] (ii) carbonylative cyclization between an amino-alcohol and 2-bromobenzaldehyde using palladium catalysis under controlled pressure;[5] (iii) intramolecular nucleophilic displacement of halides with oxygen atom as nucleophile;[6] and (iv) cationic cyclization involving *N*-acyliminium species.[7,8]

As a further development of our search on the synthetic



Scheme 1. Retrosynthetic sequence leading to chiral bicyclic lactam monomers **C** or **D** and corresponding chiral dimers **B**.

Keywords: amino-alcohol; *N*-acyliminium ion; bicyclic lactam; cationic cyclization; oxazole; oxazine; oxazepine; isoindolinone.

* Corresponding author. Tel.: (+033) 02-32-74-44-03; fax: (+033) 02-32-74-43-91; e-mail: adam.daich@univ-lehavre.fr

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utility and reactivity on polyheterocyclic systems containing an isoindolone moiety fused to oxazaheterocycles,[9] we wish to present herein the synthesis of related oxazolinoisoindolinones **5**–**7**, oxazinoisoindolinones **12**–**15** and oxazepinoisoindolinone **19** systems.

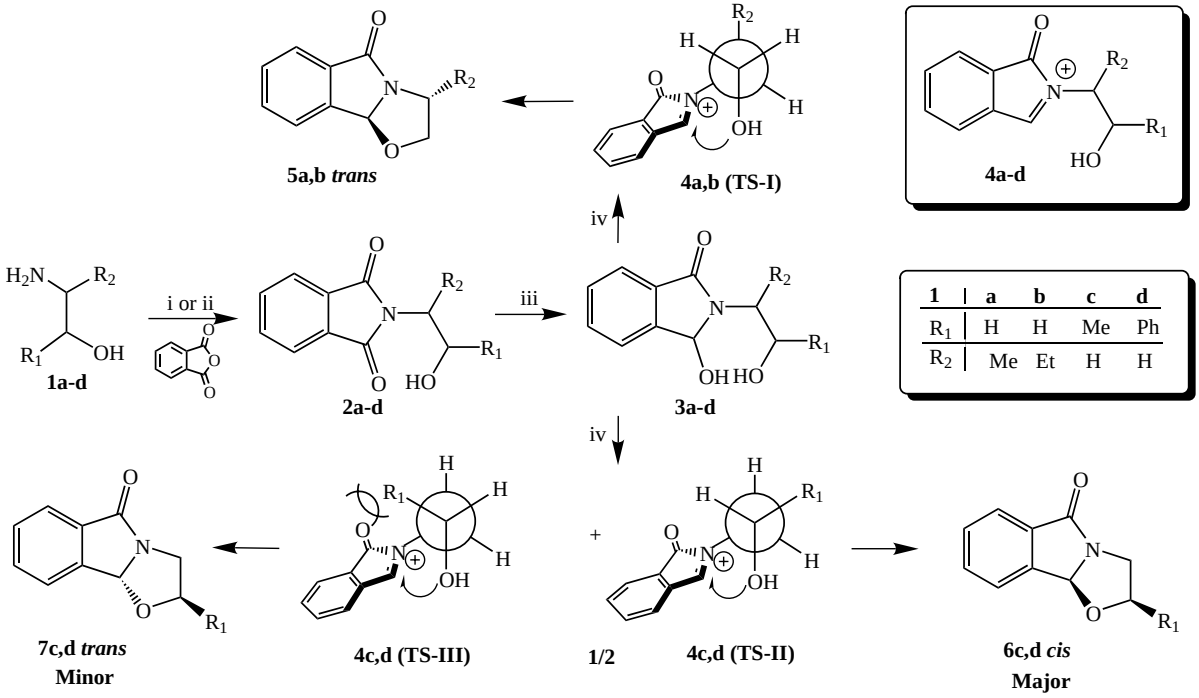
2. Results and discussion

Because we have outlined in our previous paper, using the *N*-acyliminium ion chemistry, the best formulation leading to chiral dimers **B** or corresponding chiral monomers **C** or **D** as shown above in a retrosynthetic sense in Scheme 1, we wish to use herein the same *N*-acyliminium ion methodology to access a large assembly of the title bicyclic lactams. The key step of this synthetic sequence was, in an ultimate reaction, an intramolecular formation of a carbon–oxygen bond in an acidic medium by cationic cyclization with an oxygen atom as internal nucleophile.

As shown in Scheme 2, the requisite α-hydroxylactam derivatives **3a**–**d**, as *N*-acyliminium ion precursors, were obtained in two steps from phthalic anhydride and β-amino-alcohol **1a**–**d**, by condensation under azeotropic removal of water conditions,[10] or by thermal amino-anhydride condensation at 200°C, followed by selective sodium borohydride reduction under mild conditions. In all cases, a regular addition of ethanolic hydrogen chloride solution was necessary to avoid the formation of the opened amide-alcohol as already mentioned elsewhere.[11,12]

The well known imides **2a**–**d** were isolated by distillation (**2b**) or recrystallization (**2a**,**c**,**d**) in comparable yields (92–96%).[13–19] The hydroxylactams **3a**–**d**, were obtained as a 1/1 mixture of two diastereomers (determined by ^{1}H NMR study) in a range of 56–95% yields. The separation of these diastereomers was only performed by chromatography on silica gel column for **3a** (56%) and **3d** (78%).

According to our previous work in the chiral series,[9b] hydrochloric acid (Method I) and trifluoroacetic acid (Method II) are good catalysts for the intramolecular α-oxoamidoalkylation. So, subjection of hydroxylactam **3a** to hydrochloric acid in chloroform (24 h) or trifluoroacetic acid in dichloromethane (2 h) at room temperature afforded a racemate **5a** (R_1 = H, R_2 = Me) in 80% yield. This product, which was identical to **D** (Scheme 1),[9b] showed a *trans* configuration and resulted from an intramolecular cyclization of the *N*-acyliminium intermediate **4a** in (**TS-I**) (Scheme 2). During this process, the oxygen atom attacks the iminium ion when the OH group is *anti* to the methyl one to produce the *trans* racemate **5** in accordance with our previous work in the chiral series.[9] Taking into account that ethyl group (**3b**) related to the methyl one (**3a**) gave same results via **4b** in (**TS-I**) (Scheme 2), we decided to examine the effect of the position and the nature of different groups R_1 and R_2 in the starting precursors **3c**,**d** on the cyclization step. Thus, as depicted in Scheme 2 hydroxylactam **3c** (R_1 = Me and R_2 = H) upon acidic treatment (Method I or II) gave the *cis*/*trans* mixture of two diastereomers **6c**/**7c** in a 2/1 ratio in 89% yield. According to the same method, **3d** (R_1 = Ph and R_2 = H) produced the 2/1 mixture of **6d**/**7d** in 62% yield. Compounds **6c** and **7c** as a racemate have been previously reported in the same ratio in a 30% yield from (±)-threonine and phthalic anhydride in a six- or seven-step sequence (two pathways).[20]



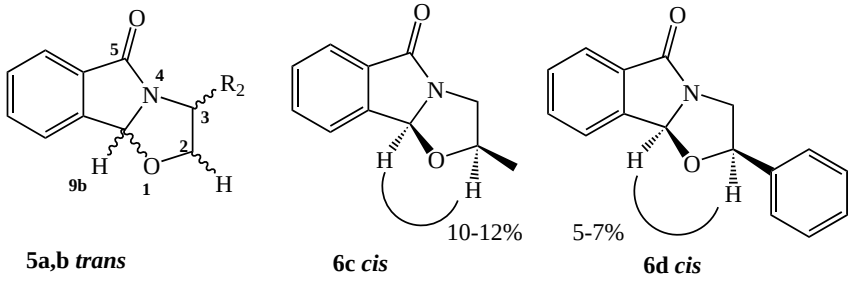
Scheme 2. *Reagents and conditions*: (i) toluene, reflux, Dean–Stark; (ii) heat at 200°C; (iii) 1.5 equiv. of $NaBH_4$, MeOH, −5 to 0°C then 10% HCl in ethanol; (iv) Method I: HCl, chloroform, 24 h; Method II: TFA, dichloromethane, 2 h.

These products **6d**/**7d** and their methyl derivatives **6c**/**7c**, were easily separated by chromatography on a silica gel column using a mixture of *i*-hexane/ethyl acetate as eluent, and their structures were established by spectroscopic analyses, ^1H, ^{13}C NMR and IR. The ^1H NMR spectra of **5**–**7** showed a typical H_{9b} proton signals ($\delta = 5.84$–7.87 ppm) and H_9 aromatic signals ($\delta = 7.77$–7.88 ppm as doublet with coupling constant of $J = 7.2$–7.5 Hz), of the fused isoindolone systems. These protons were in general shifted downfield compared to the same of their congeners **3a**–**d** which shifted at $\delta = 5.50$–6.04 ppm (H_3) and $\delta = 7.33$–7.56 to 7.58–7.68 ppm (H_4), respectively.

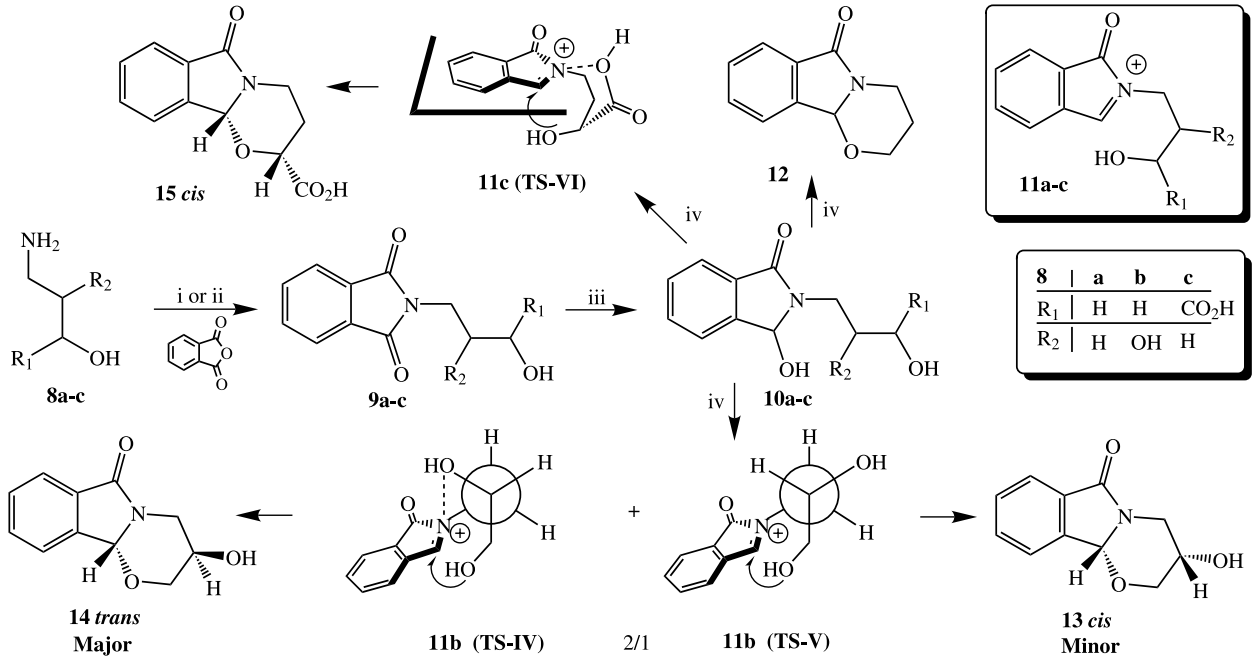
These data, the microanalyses, and the coupling GC–MS clearly confirmed the proposed structures of products **5**–**7**. Finally, the relative stereochemicals relationship were established using selective NOE difference measurements (Scheme 3). In fact, for **6c**,**d** (*cis*) as major products (Scheme 2) a strong NOE effect was observed confirming the *cis*-orientation of H_2 and H_{9b}. This result can also be explained by assuming the more stability of the transition state (**TS-II**) in which the attack of *N*-acyliminium ion **4c**,**d** by oxygen atom is being favoured from the *anti*-direction to the R_1 (methyl or ethyl) group. According to same Cram's rule, the less stable (**TS-III**) would lead to minor products **7c**,**d** as *trans* isomers (Scheme 2).[21]

Under the light of these results it seems that the position of the substituent group constitutes the key of the cyclization step. Actually, in the case of an α-substitution ($R_1 = H$; $R_2 = Me$, Et) the cyclization leads specifically to the *trans* racemate **5a**,**b** while in the case of a β-substitution ($R_1 = Me$, Et; $R_2 = H$) the reaction becomes diastereoselective since a *cis* (**6**) and *trans* (**7**) of a mixture product, in a 2/1 ratio, is obtained.

To establish the generality and versatility of this synthetic approach, the elaboration of different novel six and seven *N*,*O*-heterocyclic systems, was explored. So, the requisite α-hydroxylactams **10a**–**c** were obtained similarly from phthalic anhydride and β-amino-alcohol **8a**–**c** (Scheme 4).



Scheme 3. NOE difference determination of the relative geometry of 2-substituted oxazolinoisoindolinones **5**–**7**.



Scheme 4. *Reagents and conditions*: (i) toluene, reflux, Dean–Stark; (ii) heat at 200°C; (iii) 1.5 equiv. of $NaBH_4$, MeOH, −5 to 0°C then 10% HCl in ethanol; (iv) Method I: HCl, chloroform, 24 h; Method II: TFA, dichloromethane, 2 h.

In the first set of our cationic cyclization with oxygen atom as internal nucleophile, hydroxylactam **10a** was subjected to trifluoroacetic acid in dichloromethane at room temperature for 2 h (Method II). The ^{1}H NMR and GC–MS analysis of crude reaction product indicated the presence of the sole expected 2,3,4,10*b*-tetrahydro[1,3]-oxazino[2,3-*a*]isoindol-6-one (**12**) which was isolated as a solid after recrystallization from dry ethanol in 85% yield.

Interestingly, afterwards we decided to study the effect of the presence of another oxygen atom nucleophile (compounds **10b** (R_1 = H; R_2 = OH) and **10c** (R_1 = CO_2H; R_2 = H)), on the selectivity of the cyclization process.

So, treatment of hydroxylactam **10b** according to Method I or II, gave the 1/2 separable mixture of **13**/**14** diastereomers in 95% yield. Their relative *cis*/*trans* stereochemistry was confirmed by NOE difference experiments (Scheme 5). The inversion of the selectivity of the cyclization reaction, **6c**/**7c** (2/1 ratio) compared to **13**/**14** (1/2 ratio), could be probably due to the fact that the conformation in the transition state (**TS-IV**) (Scheme 4) should be more stable than the transition state in the (**TS-V**), since an interaction between the oxygen doublet of the hydroxy function and the *N*-acyliminium cation exists in (**TS-IV**).

At this stage, it is worth mentioning that we have never isolated the 2-hydroxymethyl-2,3-dihydrooxazolo[2,3-*a*]-9b*H*-isoindol-5-one (**16**) which could resulted from a cyclization with oxygen atom at C_β as internal nucleophile. These results were in accordance with the Baldwin rules,[22] since a 6-*endo*-trigonal ring forming process was favoured rather than a 5-*endo*-trigonal one.

As an extension, hydroxylactam **10c** (in which a carboxylic acid function is bearing by the C_α adjacent to the terminal OH function) in a similar manner as above afforded the exclusive **15** in 89% yield. The *cis* relative position of the angular proton H_{10b} with H_2 proton was determined by NOE difference measurements (8%) (Scheme 5). This can also be rationalized by the oxygen atom attack of the *N*-acyliminium ion in **11c** as shown in Scheme 4.

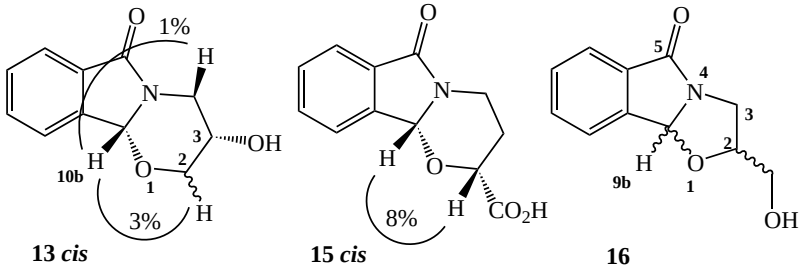
The synthesis of the [1,3]oxazepino[2,3-*a*]isoindol-7-one **19** (Scheme 6) constitutes a generalization of the oxygen-cationic cyclization process. In a three step sequence, similarly as outlined above from phthalic anhydride and 4-aminobutanol (**17**) we prepared the bicyclic lactam **19** in an overall of 65% yield.

3. Conclusion

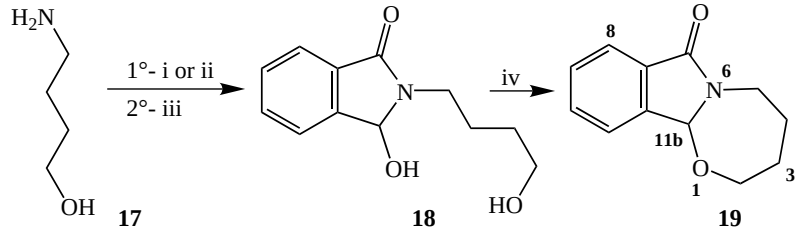
We have developed a simple and efficient route to the fused oxazoloisoindolinones **5**–**7**, oxazinoisoindolinones **12**–**15** and oxazepinoisoindolinone **19** systems by protic acid induced intramolecular cyclization of *N*-acyliminium ion precursors.[23] These latter were obtained easily in two steps from phthalic anhydride and amino-alcohols. Furthermore, the chemoselectivity of these reactions is discussed and the probable intermediates leading to stereomers are proposed.

Supplementary material

The data including chemical and physical characteristics of all products may be obtained at the following e-mail address: adam.daich@univ-lehavre.fr



Scheme 5. NOE difference determination of the relative geometry of 2- or 3-substituted oxazinoisoindolinones **13** and **15**.



Scheme 6. *Reagents and conditions*: (i) phthalic anhydride, toluene, reflux, Dean–Stark; (ii) phthalic anhydride, heat at 200°C; (iii) 1.5 equiv. of $NaBH_4$, MeOH, −5 to 0°C then 10% HCl in ethanol; (iv) Method I: HCl, $CHCl_3$, 24 h; Method II: TFA, CH_2Cl_2, 2 h.

Acknowledgements

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23. Procedures for synthesis of α-hydroxylactams (**4a–d**, **11a–c**, **18**) and corresponding bicyclic lactams (**5–7**, **12–15**, **19**).

General procedure for the synthesis of α-hydroxylactams (**4a–d**, **11a–c** and **18**). To a stirred solution of *N*-alkylated phthalimide (10 mmol) in dry methanol (40 mL) at −5 to 0°C was added by portions 1.5 equiv. of sodium borohydride (0.567 g, 15 mmol). After addition of sodium borohydride, three drops of ethanolic hydrochloric acid solution was added during 10 min (prepared from one drop of concentrated hydrochloric acid in 1 mL of ethanol) until the reaction was complete (30–40 min, monitored by TLC). The excess of sodium borohydride was decomposed by careful addition of 10% hydrochloric acid solution to pH 2. After removal of the solvent, the residue was diluted with water (40 mL) and extracted with 30 mL of dichloromethane. The organic layers were washed with water, brine, dried over sodium sulfate and evaporated under reduced pressure. The resulting crude product was purified by chromatography on silica gel column or by recrystallization to give pure ω-carbinol lactam **4a–d**, **11a–c** or **18**.

General procedure for cationic cyclization in acidic medium: **Access to bicyclic lactams 5–7**, **12–15** and **19**. To a stirred solution of hydroxylactam (**4a–d**, **11a–c** or **18**) (10 mmol) in 10 mL of chloroform (Method I) or dry dichloromethane (Method II) was added two to three drops of concentrated hydrochloric acid (Method I) or 5 mL of trifluoroacetic acid (Method II) and allowed to react at room temperature for 24 or 2 h, respectively. After complete reaction at room temperature under stirring, the reaction mixture was diluted with water (30 mL) and neutralized carefully with 10% sodium hydroxide aqueous solution. The solution was extracted twice with dichloromethane or chloroform (20 mL). The organic layer was washed with water, brine, separated, dried over magnesium sulfate and evaporated under reduced pressure. The resulting crude residue was purified by chromatography or recrystallization to give the bicyclic product **5–7**, **12–15** or **19** in good yields.