Evaluation of *N*-Hydroxymethylphthalimide in Alkaline Medium: Novel Entry to the Tricyclic [1,3]Oxazepine core *via* an Intramolecular π and *O*-Cationic Cyclization

Armelle Cul[a], Abderrahim Chihab-Eddine[b], Anthony Pesquet[a], Štefan Marchalín[c] and Adam Daïch[a]*

[a] Laboratoire de Chimie, URCOM, EA 3221, Faculté des Sciences & Techniques de l'Université du Havre, B.P: 540, 25 Rue Philippe Lebon, F-76058 Le Havre Cedex, France
[b] Laboratoire de Bio-Organique, Département de Chimie, Faculté des Sciences, Université Ibnou Zohr, B.P:28/S, Agadir, Maroc
[c] Department of Organic Chemistry, Slovak University of Technology, Radlinského 9, SK-812 37 Bratislava, Slovakia
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Fused isoindolo[1,3]benzo(or thieno)oxazepines **8a,b** and one of their positional isomers aromatic tricyclic *N,O*-acetals **13b** are reported to occur efficiently in a three-step sequence from *N*-hydroxymethylphthalimide (**6**). The key step of this methodology is the intramolecular arylation of an endocyclic and/or exocyclic *N*-acyliminium cation. The mechanism leading to these species, in particular to a tricyclic lactam **13b**, is discussed.

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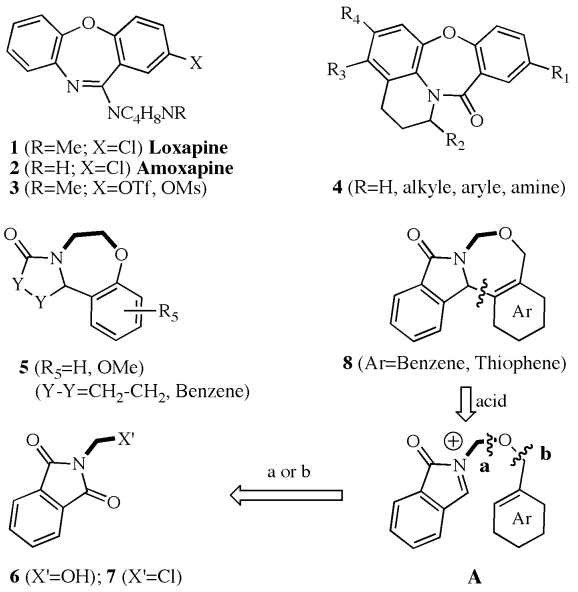
Introduction.

The development of simple and general synthetic routes for wide ranges of organic compounds from readily available reactants constitutes one of the major challenges in modern organic chemistry. Seven-membered ring systems containing two heteroatoms (*N* and *O*), such as the oxazepines, are key classes of organic products with numerous applications in biology. In fact, [1,4]benzoxazepines with such scaffolds such as the well-established representatives Loxapine (**1**) [1] and Amoxapine (**2**) [2] are neuroleptics with a general pattern of pharmacological activity [1], including both neuroleptic [2] and antidepressant activity [3,4], respectively (Scheme 1). Furthermore, the 2-TfO- and 2-MsO-dibenzoxazepine analogues **3** exhibit clinically interesting properties as Clozapine-like atypical antipsychotics [5]. Other compounds exemplified by quino[1,4]benzoxazepines **4** which are structurally closely related to the above, have good inhibitory activity against the reverse transcriptase of HIV-1 [6]. Because of the great potential of these types of structures, efforts continue to be made particularly in the synthesis of a new class of [1,4]benzoxazepines **5** in which a pyrrolidinone [7,8] or isoindolone [7] moiety constitutes a nitrogen atom source.

Scheme 1



1 (R=Me; X=Cl) **Loxapine**
2 (R=H; X=Cl) **Amoxapine**
3 (R=Me; X=OTf, OMs)

4 (R=H, alkyle, aryle, amine)

5 (R_5=H, OMe)
(Y-Y=CH_2-CH_2, Benzene)

8 (Ar=Benzene, Thiophene)

6 (X'=OH); **7** (X'=Cl)

A

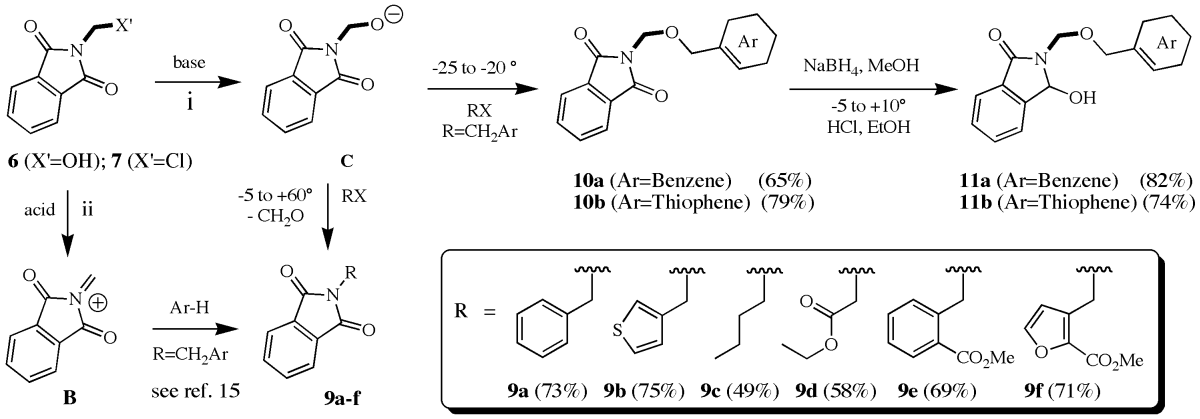
Structures of representative active [1,4]benzoxazepines **1-5** and the retrosynthetic scheme leading to the related [1,3]benzoxazepines **8**.

However, if fused [1,4]benzoxazepines are well documented, the structurally related [1,3]benzoxazepines fused to aromatic or non aromatic ring are little known a fact that is reflected in the few reports in the literature of their syntheses, uses and biological evaluation. To date, several synthetic routes for their elaboration have been described: The most versatile strategy to accede this type of *N,O*-heterocycles, is the cyclodehydration reaction between a dicarbonyl compound and an amino-alcohol [9]. Palladium catalyzed heteroannulation cascades of allenes [10], and aryl(or alkyl)thio radicals [11] and cationic [12] cyclizations involving *N*-acyliminium precursors are other approaches reported. In all these cases, the reported [1,3]oxazepines belong to the 7,5-fused bicyclic lactams commonly known as *N,O*-acetals which have been used principally as important synthetic intermediates to accede Morphan alkaloid cores [9a] and (±)-Adalinine alkaloids [9b], and as valuable building blocks for peptidomimetics [12b], respectively.

Results and Discussion.

In the course of our continuing efforts towards the evaluation of *N*-arylthioalkylimides [13] and *N*-aryloxoalkylimides [14] functionalities in acidic medium, we report herein our preliminary findings from our investigations on *N*-arylmethyloxomethylphtalimides as *N*-acyliminium ions precursors under acid conditions. To our

Scheme 2



Reagents : (i) 1.2 equiv. of MeONa (K_2CO_3 or NaH), DMF (THF or 1,4-dioxane), -5 to 0 °, 1 h; (ii) conc. H_2SO_4 ($BF_3.Et_2O$, $AlCl_3$, $ZnCl_2$, $SnCl_4$, $SbCl_5$ or strong acid as $AgSbF_6$, $AgBF_4$), neat (CH_2Cl_2, di-isopropyl ether or CS_2), then Ar-H. Fore more details see ref. 15.

knowledge no work has been done on the chemistry of these systems, and interestingly, all studies in this area concern only the *N*-phenyloxoethylimides [7,8], with the exception of our previous work dealing with the synthesis of isoindolo[1,3]benzoxazines using *N*-chloromethylphthalimide (**7**) as starting metrial [14].

As our tricyclic benzoxazepine targets could be obtained from *N*-hydroxymethylphthalimide (**6**) or corresponding halides **7**, *via* the π-cationic cyclization of the *N*-acyliminium ion intermediates **A** shown in Scheme 1, our initial experiments have centred on the evaluation of the reactivity of *N*-hydroxymethylphthalimide (**6**). The behaviour of substrates **6** and **7**, in acidic medium, is well-established and leads to the exocyclic *N*-acyliminium ion **B** which can be trapped by various external aryl systems to furnish *N*-aralkylphthalimides **9a-f** in good yields (Scheme 2) [15].

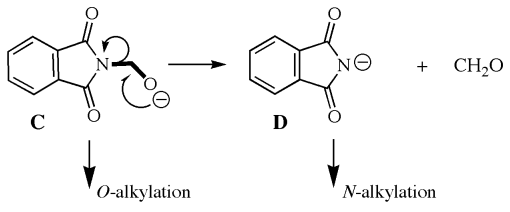
Since *N*-hydroxymethylphthalimide (**6**) reacts with amines as a nitrogen base (R_1R_2NH) without additional co-solvent, to give successfully, *via* dehydration, only the *N*,*N*-dialkylaminomethylphthalimide [16], the coupling of alcohol **6** with halide (RX) in the presence of a mineral base was examined. To our surprise benzyl chloride with 1.2 equiv. of sodium methoxide in dry DMF at room temperature for 6 h of reaction, give only the well-known *N*-benzylphthalimide (**9a**) in appreciable 73% yield [17]. In spite of the apparent simplicity of this process which required the transformation of the alkoxide **C** into the corresponding imidate **D** as the consequence of the extrusion of formalin (see Scheme 3) followed by a nucleophilic displacement of halide with the nitrogen atom of **D**, several experimental parameters were considered. Thus, the variation of the solvent (THF, 1,4-dioxane) and the nature of the base (K_2CO_3, NaH) did not change the reaction profile, and in all these combinations only the *N*-alkylated product **9a** resulting from a tandem formalin elimination/nucleophilic substitution was isolated in comparable yield.

Attempts to extend this reaction to heteroaromatic, alkyl, functionalized alkyl, functionalized aromatic and functionalized heteroaromatic halides was successful and produced only the corresponding *N*-alkylated products **9b** (75%) [18], **9c** (49%) [19], **9d** (58%) [20], **9e** (69%) [21], and **9f** (71%) [21], respectively. In light of these results, its seems that the imidate anion **D** is more stable than the alcoholate one **C** under basic conditions at these temperatures.

Furthermore taking into account that Wada *et al.* [22], has esterified alcohol **6**, without loss of formalin, with acid chloride derivative at 0 °C in the presence of triethylamine as base, the reaction of alcohol **6** with benzyl chloride and a base was examined again at different temperatures. Even if at –5 to +60 °C we isolated exclusively the above *N*-alkylated product **9a**. When the temperature was decreased at –25 to –20 °C, in contrast, the *O*-alkylation occurred leading to the expected product **10a** in 65% yield [23]. It is worth mentioning that under these conditions more than 48 h of reaction was necessary and, in all runs, the *O*-alkylated product **10a** was accompanied with small amounts of the *N*-alkylated product **9a** [24].

Application of this procedure to 3-bromomethylthiophene, similarly, give a *N*-(thien-3-yl-methyloxomethyl)-phthalimide (**10b**) as the sole reaction product in 79%

Scheme 3



Transformation of alcoholate **C** into imidate **D** obtained in basic conditions from *N*-hydroxymethylphthalimide (**6**).

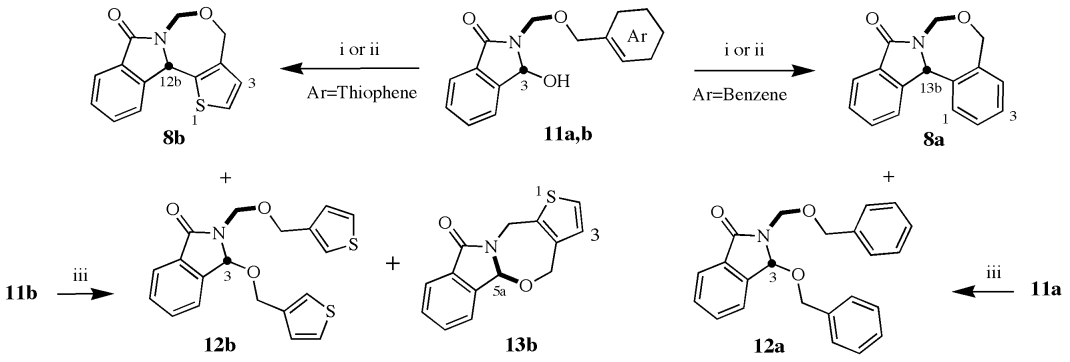
yield. Mechanistically, it appears that the decomposition of alcoholate **C** into imidate **D** (Scheme 3) is not effective since the alcoholate, which is required for the *O*-alkylation process, is more stable at lower temperature [25].

Having isolated the *O*-alkylated imides **10a,b**, the regioselective reduction of one carbonyl of imide function proceeded smoothly with a large excess of $NaBH_4$ (6 equiv.) in methanol and gave the desired α-hydroxylactam **11a** after silica gel chromatography with CH_2Cl_2/hexane (9:1) as eluent (82%) and **11b** after recrystallization from dry ethanol (74%). In all these reduction processes, regular addition of ethanolic hydrogen chloride solution (10%) was necessary to avoid the formation of the opened amide-alcohol as already noted [26].

According to our previous work in this field, *p*-toluenesulfonic acid and trifluoroacetic acid are good catalysts for the intramolecular amidoalkylation. Thus, the subjection of the above α-hydroxylactam **11a**, as a model of *N*-acyliminium ion precursor, to these acids [27] under various conditions afforded in term two kinds of compounds (Scheme 4) and the results are summarized in Table 1.

These results deserve comment. Contrary to *N*-aryloxomethylamidals which led exclusively to isoindolo[1,3]-benzoxazines [14], α-hydroxylactam **11a** used in this work gives a mixture of two products which were identified as the isoindolo[1,3]benzoxazepine **8a** and the *N,O*-diacetal **12a**. The ratio and yield of these depend on the reaction temperature (entries 3, 4), the nature (entries 4, 7) and the quantity (entries 1, 2, 3 and 5, 6, 7) of the acid used. The product **8a** as the major component is the result of the intramolecular arylation of the *N*-acyliminium ion **E** (Scheme 5). Furthermore, the stability of a benzyl alcohol obtained from a tandem cleavage/protonation of the etheroxyde linkage of **11a** in acidic conditions combined with the good nucleophilicity of the oxygen atom [12,26b] constitutes a significant intermolecular competing process leading to **12a** to the detriment of the classical π-cationic

Scheme 4



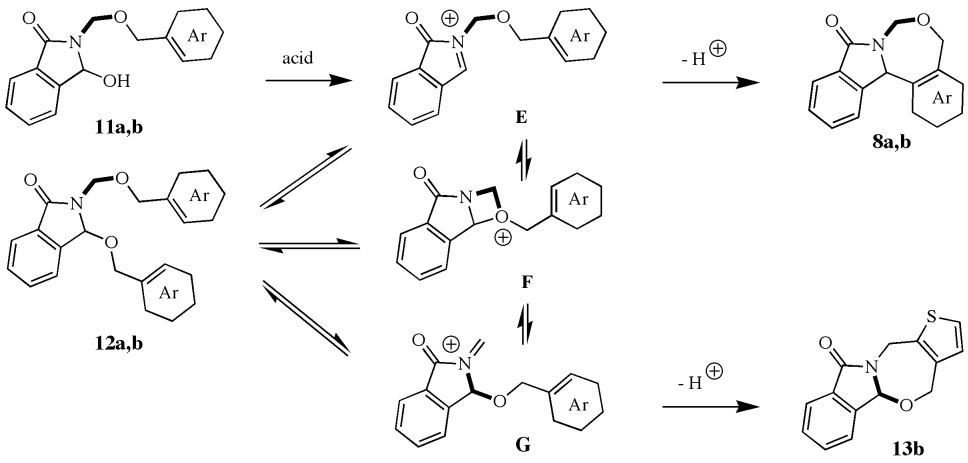
Reagents and conditions: (i) PTSA, CH_2Cl_2, rt, 3 h (see Table 1); (ii) TFA, CH_2Cl_2, rt, 2 h (see Table 1); For Ar=benzene, (iii) 1.2 equiv. of NaH, DMF, 1 equiv. of benzyl chloride, rt, 24 h (81%). For Ar=thiophene, (iii) 1.2 equiv. of NaH, DMF, 1 equiv. of 3-bromomethylthiophene, rt, 24 h (75%).

Table 1
Reaction Conditions and Yield of Products Obtained from the Reaction of α-Hydroxylactams **11a,b** and Different Acids

Entry	Precursor	Acid, quantity	Conditions	Products			Yield of reaction % [a]	Ratio of products % [b]
1	**11a**	PTSA, 1.0 equiv.	CH_2Cl_2, rt, 3 h	-	-	-	Decomposition [c]	-
2	"	"	CH_2Cl_2, 0 °C, 4 h	-	-	-	"	-
3	"	PTSA, catalytic	CH_2Cl_2, 0 °C, 7 h	**8a**	**12a**	-	37	1.4/1
4	"	"	CH_2Cl_2, rt, 3 h	**8a**	**12a**	-	42	1.5/1
5	"	TFA, neat	rt, 3 h	-	-	-	Decomposition [c]	-
6	"	TFA, 1.0 equiv.	CH_2Cl_2, rt, 2 h	-	-	-	"	-
7	"	TFA, catalytic	"	**8a**	**12a**	-	53	2/1
8	**11b**	PTSA, catalytic	"	-	**12b** [d]	-	34	0/1/0
9	"	TFA, catalytic	"	**8b**	**12b**	**13b**	55	5.5/1.5/1

[a] The reactions were performed on 3-6 mmol using 10 ml of dry CH_2Cl_2, and the yield corresponds to the isolated products or purified products mixture; [b] The ratio of isomers was determined by ^1H NMR spectrum analysis; [c] All starting material was decomposed in acidic conditions; consequently, only the benzyl alcohol and 3-thiophenemethanol were isolated; [d] Taking into account that two equivalents of starting material **11b** were necessary to form **12b**, this product may be obtained at max efficiency in 50% yield.

Scheme 5



Simplified reaction mechanism for the isomerization of the classical endocyclic *N*-acyliminium ion **E** leading to heterocycles **8** and **13**.

cyclization leading to the product **8a**. The structure of compounds **8a** and **12a** have been established by ^{1}H and/or ^{13}C-NMR spectroscopy as well as by the coupling GC-MS. Moreover, the *O*-alkylation reaction of hydroxylactam **11a** at the hydroxyl group according to our report [28] (using 1.2 equiv. of NaH, dry DMF and 1 equiv. of benzyl chloride at 0 °C to rt for 24 h) give **12a** in 81% yield (Scheme 4) thus confirming the structure proposed for this product **12a** [29].

From these results, it was of interest to investigate this cyclization in a heterocyclic series. Subjecting the hydroxylactam **11b** to cyclization (conditions (i), entry 8) gave exclusively product **12b** (34%) which was formed in the same manner as **12a**. Its structure was equally confirmed by the univocally classical *O*-alkylation starting from **11b** (Scheme 4, Table 1, 75% yield) [29]. Furthermore, the hydroxylactam **11b** was allowed to react under conditions (ii) as outlined above (entry 9, table 1). Interestingly, spectroscopic analysis of the crude product by ^{1}H NMR revealed the product to be a 5.5:1.5:1 mixture of three components as [1,3]thienoxazepine **8b**, *N,O*-diacetal **12b** and tricyclic lactam **13b**, respectively (55%). Attempts of separation by chromatography give only **13b** as a solid in pure form while **8b** and **12b** remain inseparable, whatever the attempts for their separation, in a ratio of approximatively 4:1.

The assignment of these structures was made on the basis of coupling GC-MS, elemental analyses and other spectroscopic properties. The IR spectra of a mixture of **8a**+**12a** and **8b**+**12b** or pure products **12a**, **12b** and **13b** indicated the absence of an O-H stretch. The ^{1}H NMR spectra of **12a,b** showed three methylene groups instead of two for their hydroxylactam congeners **11a,b**. We found also that H_3 signal on a tertiary carbon of **12a,b** were shifted downfield compared to the same protons in corresponding alcohols **11a,b** ($\Delta\delta$=+0.12 and +0.07 ppm respectively). In a similar fashion, the same angular protons H_{13b} (δ=6.02 ppm for **8a**) and H_{12b} (δ=6.01 ppm for **8b**) appear as singlets without significant change (δ=5.95 ppm for **11a** and **11b**). In contrary to product **13b**, the angular proton appears at δ=6.11 ppm comparable to those of **12a,b**. Likewise, the ^{13}C NMR spectra of **13b** revealed the presence of an additional quaternary carbon as the consequence of the cyclization process. Furthermore, an important deshielding of the angular carbon of component **13b** was observed (δ=89.7 ppm instead of the range 80.7 to 86.4 ppm for other products **8a,b**, **11a,b** and **12a,b**) which is due to the proximity of the oxymethylene group [12a].

As depicted mechanistically in Scheme 5, [1,3]benzoxazepines **8a,b** are obtained classically through arylation of the *N*-acyliminium ion **E** generated in acidic medium from **11a,b**. Formation of tricyclic lactam **13b**, could be explained by isomerization of the endocyclic cation **E** into the exocyclic one **G** *via* the azaoxonium ion **F**, followed ultimately by intramolecular π-cationic cyclization. Interestingly, related cations which are in equilibrium *via* a cyclic aza-sulfonium ion obtained from an atypical intramolecular α-thioamidoalkylation and leading to isomeric [1,3]benzothiazines are put in evidence recently by us [13b]. Otherwise, the only report concerning similar phenomenon which using a tandem as aza-Cope isomerization/intramolecular *O*-cationic cyclization was pointed in literature [30].

Conclusion.

We have shown that *N*-hydroxymethylphthalimide (**6**) in alkaline medium and depending essentially on the reaction temperature give selectively the *N*- or *O*-alkylated phthalimide products in good yields. These latter, as *N*-acyliminium ion precursors, lead to fused [1,3]oxazepines **8** and to a tricyclic lactam **13** through an intramolecular arylation of an endocyclic **E** and exocyclic **G** *N*-acyliminium ions, respectively. These species are in aquilibrium *via* the newly cyclic azaoxonium ion **F**.

EXPERIMENTAL

All melting points were measured on a Boetius micro hot-stage and are uncorrected. The infrared spectra of solids (potassium bromide) and liquids (neat) were recorded on a Perkin Elmer FT-IR paragon 1000 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (200 MHz) instrument in deuteriochloroform unless otherwise indicated and chemical shifts (δ) are expressed in ppm relative to TMS as internal standard. Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F 254 (Merck) and the spots visualised using an ultraviolet lamp or iodine vapour. Mass spectral measurements were recorded on an AEI MS 902 S spectrophotometer. Elemental analyses were carried out by the microanalysis laboratory of INSA, F-76130 Mt. St. Aignan, France.

General Procedure for *N*-Alkylation of *N*-Hydroxymethylphthalimide (**6**).

To a stirred solution under an atmosphere of dry argon of *N*-hydroxymethylphthalimide (**6**) (1.77 g, 10 mmol) in 10 mL of dry DMF was added 0.65 g (12 mmol) of sodium methoxide. After stirring for 20 min at –5 to +60°, 10 mmol of halide RX (see text for details) dissolved in 10 mL of dry DMF was added dropwise over a period of 15 min. The mixture was then allowed to react at the same temperature for 6 h and hydrolyzed. The resulting solid was collected by filtration and recrystallized from ethanol to give the expected imide **9a-f** in 49 to 75% yield. In the case of **9c**, the solution after hydrolysis was concentrated under reduced pressure, extracted with dichloromethane, dried over magnesium sulfate and evaporated to give **9c** as an oil in 49% yield. The data of these products correspond to that reported in literature (see text).

N-(2-Methoxycarbonylfur-3-yl-methyl)phthalimide (**9f**).

This product was isolated in a yield of 71 % as a white solid; mp 147-149° (ethanol); IR (KBr): ν 3026, 2096, 1715, and 1702 cm^{-1}; ^{1}H NMR: δ 3.93 (s, 3H, OMe), 5.10 (m, 2H, CH_2-N), 6.39 (d, *J*=1.5 Hz, 1H, H_4-furane), 7.41 (d, *J*=1.5 Hz, 1H, H_5-furane), 7.69-7.74 (m, 2H, $H_{phthalimide}$), 7.81-7.86 (m, 2H, $H_{phthalimide}$); ^{13}C NMR: δ 33.5 (CH_2), 52.1 (OCH_3), 112.9 (CH), 123.6 (2CH), 129.9 (C), 132.0 (C), 134.3 (2CH), 140.5 (2C), 145.5 (CH), 159.4 (C=O), 167.9 (C=O); MS (m/z) 285 (M^+).

Anal. Calcd. for $C_{15}H_{11}NO_3$: C, 63.16; H, 3.88; N, 4.91. Found: C, 63.02; H, 4.00; N, 4.78.

General Procedure for *O*-Alkylation of *N*-Hydroxymethylphthalimide (**6**).

This reaction was performed in a similar manner as above except that the reaction temperature was maintained at –25 to –20°. After 52 h, the mixture was poured onto crushed ice and the small amount of precipitate was extracted with diethyl ether several times. After the classical work up of the organic layer, the residue obtained was purified by chromatography on silica gel column using a mixture of dichloromethane/hexane (4:1) as eluent to give the *O*-alkylated product **10a** and **10b**. Product **10a** was accompanied with the *N*-alkylated **9a** in a small amount (< 8% yield).

N-(Benzyloxymethyl)phthalimide (**10a**).

This product was obtained as a white solid in 65 % yield; mp 84-85° (ethanol) (lit. [23], mp 80-81° (isopropyl ether)); IR (KBr): ν 3016, 2090, and 1708 cm^{-1}; ^{1}H NMR: δ 4.61 (s, 2H, O-CH_2), 5.16 (s, 2H, CH_2-O), 7.15-7.34 (m, 5H, $H_{aromatic}$), 7.68-7.75 (m, 2H, $H_{phthalimide}$), 7.80-7.86 (m, 2H, $H_{phthalimide}$); ^{13}C NMR: δ 66.9 (CH_2), 71.5 (CH_2), 123.8 (2CH), 127.8 (2CH), 128.1 (CH), 128.5 (2CH), 131.9 (C), 134.5 (2CH), 137.4 (2C), 168.1 (2C=O); MS (m/z) 267 (M^+).

Anal. Calcd. for $C_{16}H_{13}NO_3$: C, 71.89; H, 4.90; N, 5.24. Found: C, 71.77; H, 4.82; N, 5.22 .

N-(Thien-3-yl-methyloxymethyl)phthalimide (**10b**).

This product was obtained as a white-yellow solid in 79 % yield; mp 115-118° (ethanol/water); IR (KBr): ν 3018, 2095, and 1702 cm^{-1}; ^{1}H NMR: δ 4.67 (s, 2H, O-CH_2), 5.23 (s, 2H, CH_2-O), 7.05 (d, *J*=4.7 Hz, 1H, H_4-thiophene), 7.18-7.35 (dd, *J*=3.1 and 2.3 Hz, 2H, $H_{2,5}$-thiophene), 7.68-7.78 (m, 2H, $H_{phthalimide}$), 7.81-7.94 (m, 2H, $H_{phthalimide}$); ^{13}C NMR: δ 66.8 (CH_2), 67.2 (CH_2), 123.6 (CH), 124.0 (2CH), 126.4 (CH), 127.5 (CH), 132.1 (2C), 134.7 (2CH), 138.6 (C), 168.3 (2C=O); MS (m/z) 273 (M^+).

Anal. Calcd. for $C_{14}H_{11}NO_3S$: C, 61.52; H, 4.06; N, 5.12. Found: C, 61.48; H, 3.98; N, 4.99.

General Procedure for Reduction of Imides (**10a,b**).

To a mixture of 5 mmol of imide **10a** (or **10b**) in dry methanol (40 mL) at -5-0° was added sodium borohydride (1.13 g, 30 mmol) by portions during 5 min. To this mixture was added 5 drops of ethanolic hydrochloric acid solution (prepared by addition of 9 drops of concentrated hydrochloric acid into 5 mL of dry ethanol) at regular intervals of 10 min. The reaction was monitored by TLC using CH_2Cl_2 as eluent. At the end of the reaction (90 min), the excess of sodium borohydride was decomposed by careful addition of cold water (15 mL) and 10 % hydrochloric acid until pH = 4. Sodium hydrogen carbonate was added and the solvent was evaporated. The resulting residue was triturated with water and dichloromethane and the organic layer was separated, washed with water, brine, dried over magnesium sulfate and concentrated in *vacuo*. The resulting product was purified by chromatography on silica gel column or by recrystallization to give **11a** or **11b**, respectively.

N-(Benzyloxymethyl)-2,3-dihydro-3-hydroxy-1*H*-isoindol-1-one (**11a**).

This product was isolated as an colorless oil in 82 % yield after chromatography on silica gel column (CH_2Cl_2/hexane, 9:1); IR (neat): ν 3259, 3008, 2094, and 1700 cm^{-1}; ^{1}H NMR: δ 3.1

(d, *J*=10.2 Hz, 1H, OH, exchangeable with D_2O), 4.49 (s, 2H, O-CH_2), 4.88 (d, *J*= 10.9 Hz, 1H, CH_2-O), 5.04 (d, *J*=10.9 Hz, 1H, CH_2-O), 5.94 (d, *J*=10.2 Hz, 1H, CH), 7.20-7.34 (m, 5H, $H_{aromatic}$), 7.44-7.52 (m, 1H, $H_{phthalimide}$), 7.54-7.60 (m, 2H, $H_{phthalimide}$), 7.72 (d, *J*=8.1 Hz, 1H, $H_{phthalimide}$); ^{13}C NMR: δ 69.9 (CH_2), 71.5 (CH_2), 81.6 (CH), 124.5 (CH), 124.8 (CH), 128.5 (CH), 128.9 (2CH), 129.2 (2CH), 130.8 (CH), 131.3 (C), 134.1 (CH), 138.3 (C), 145.2 (C), 168.7 (C=O); MS (m/z) 269 (M^+).

Anal. Calcd. for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.26; H, 5.51; N, 5.09.

2,3-Dihydro-3-hydroxy-*N*-(thien-3-yl-methyloxymethyl)-1*H*-isoindol-1-one (**11b**).

This product was isolated as a white-yellow solid in 74 % yield after recrystallization from ethanol; mp 83-85°; IR (KBr): ν 3263, 3022, 2086, and 1695 cm^{-1}; ^{1}H NMR: δ 4.48 (s, 2H, O CH_2), 4.77 (dd, *J*=10.9 and 10.2 Hz, 2H, OH and O-CH_2), 4.94 (d, *J*=10.9 Hz, 1H, O-CH_2), 5.95 (d, *J*=10.2 Hz, 1H, CH), 7.03 (d, *J*=4.7 Hz, 1H, H_4-thiophene), 7.19-7.32 (m, 2H, H_2-thiophene an $H_{phthalimide}$), 7.43-7.55 (m, 1H, $H_{phthalimide}$), 7.57-7.69 (d+d, *J*=7.8 and *J*=3.9 Hz, H_5-thiophene and $H_{phthalimide}$); ^{13}C NMR: δ 66.0 (CH_2), 68.6 (CH_2), 80.7 (CH), 123.5 (CH), 123.8 (CH), 123.9 (CH), 126.3 (CH), 127.5 (CH), 130.0 (CH), 130.7 (C), 133.2 (CH), 138.5 (C), 144.4 (C), 168.6 (C=O); MS (m/z) 275 (M^+).

Anal. Calcd. for. $C_{14}H_{13}NO_3S$: C, 61.07; H, 4.76; N, 5.08. Found: C, 60.95; H, 4.68; N, 5.00.

General Procedure for Treatment of Hydroxylactams (**11a,b**) with Trifluoroacetic Acid or *para*-Toluenesulfonic Acid.

A solution of 6 mmol of hydroxylactam **11a** (or **11b**) in 15 mL of dry dichloromethane was stirred at required temperature (see text and table in the text part for more details) with pure trifluoroacetic acid (TFA) or paratoluenesulfonic acid (PTSA). At the end of the reaction (the reaction was monitored by TLC using dichloromethane/hexane (4:1) as eluent), the solution was concentrated *in vacuo*, diluted with CH_2Cl_2, washed successively with a saturated sodium hydrogen carbonate solution, then with water and was dried over magnesium sulfate and filtered. The solution was concentrated under reduced pressure and the residue was recrystallized and/or chromatographed to furnish **8a,b**, **12a,b**, and/or **13b**.

4,7-Dihydroisoindolo[2,1-*d*][2,4]benzoxazepin-9-(13b*H*)-one (**8a**).

This product was not isolated in pure form; ^{1}HNMR: δ 4.58 (s, 2H, O-CH_2), 4.83 (d, *J*=10.1 Hz, 1H, CH_2-N), 5.31 (d, *J*=10.1 Hz, 1H, CH_2-N), 6.02 (s, 1H, O-CH-N), 7.24-7.32 (m, 4H, $H_{aromatic}$), 7.52-7.57 (m, 3H, $H_{phthalimide}$), 7.84 (d, *J*=7.2 Hz, 1H, $H_{phthalimide}$); MS (m/z) 251 (M^+).

4,6-Dihydrothieno[2',3':5,6][1,3]oxazepino[4,3-*a*]-isoindol-8(12b*H*)-one (**8b**).

This product was not isolated in pure form; ^{1}HNMR: δ 4.57 (s, 2H, O-CH_2), 4.83 (d, *J*=10.2 Hz, 1H, CH_2-N), 5.32 (d, *J*=10.2 Hz, 1H, CH_2-N), 6.01 (s, 1H, O-CH-N), 6.94 (d, *J*=4.2 Hz, 1H, $H_{4\text{-thiophene}}$), 7.09 (d, *J*=4.2 Hz, 1H, $H_{5\text{-thiophene}}$), 7.55-7.62 (m, 3H, $H_{phthalimide}$), 7.80 (d, *J*=8.1 Hz, 1H, $H_{phthalimide}$); MS (m/z) 257 (M^+).

N-(Benzyloxymethyl)-3-benzyloxy-2,3-dihydro-1*H*-isoindol-1-one (**12a**).

This product was isolated as a white solid; mp 57-59° (diethyl ether/hexane); IR (KBr): ν 3006, 2989, and 1695 cm^{-1}; ^{1}H NMR: δ 4.12 (d, *J*=10.9 Hz, 1H, CH_2-O), 4.26 (d, *J*=10.9 Hz, 1H, CH_2-O), 4.60 (s, 2H, CH_2-O), 4.87 (d, *J*=11.0 Hz, 1H, O-CH_2-N), 5.32 (d, *J*=11.0 Hz, 1H, O-CH_2-N), 6.17 (s, 1H, O-CH-N), 7.20-7.35 (m, 10H, $H_{aromatic}$), 7.53-7.62 (m, 3H, $H_{phthalimide}$), 7.89 (d, *J*=9.4 Hz, 1H, $H_{phthalimide}$); ^{13}C NMR: δ 66.5 (CH_2), 70.1 (CH_2), 71.9 (CH_2), 86.4 (CH), 124.8 (CH), 125.1 (CH), 128.7 (CH), 128.8 (2CH), 128.9 (2CH), 129.0 (CH), 129.3 (2CH), 129.5 (2CH), 131.3 (CH), 132.5 (C), 133.4 (CH), 137.8 (C), 138.3 (C), 141.7 (C), 167.7 (C=O); MS (m/z) 359 (M^+).

Anal. Calcd. for $C_{23}H_{21}NO_3$: C, 76.86; H, 5.89; N, 3.90. Found: C, 76.59; H, 5.71; N, 3.79.

2,3-Dihydro-3-(thien-3-yl-methyloxy)-*N*-(thien-3-yl-methyl-oxymethyl)-1*H*-isoindol-1-one (**12b**).

This product was isolated as an colorless oil; IR (neat): ν 3010, 2983, and 1681 cm^{-1}; ^{1}H NMR: δ 4.14 (d, *J*=11.7 Hz, 1H, CH_2-O), 4.27 (d, *J*=11.7 Hz, 1H, CH_2-O), 4.58 (s, 2H, CH_2-O), 4.83 (d, *J*=10.9 Hz, 1H, O-CH_2-N), 5.27 (d, *J*=10.9 Hz, 1H, O-CH_2-N), 6.12 (s, 1H, O-CH-N), 6.13-6.97 (dd, *J*=1.5 and 4.7 Hz, 1H, $H_{thiophene}$), 7.02-7.09 (m, 2H, $H_{thiophene}$), 7.23-7.28 (m, 3H, $H_{thiophene}$), 7.50-7.62 (m, 3H, $H_{phthalimide}$), 7.86 (d, *J*=7.3 Hz, 1H, $H_{phthalimide}$); ^{13}C-NMR: δ 60.7 (CH_2), 65.9 (CH_2), 69.3 (CH_2), 85.4 (CH), 123.8 (CH), 124.1 (CH), 124.6 (CH), 124.8 (CH), 126.8 (CH), 127.1 (CH), 127.9 (CH), 128.1 (CH), 130.9 (CH), 132.5 (C), 133.7 (CH), 138.9 (C), 139.5 (C), 142.0 (C), 165.2 (C=O); MS (m/z) 371 (M^+).

Anal. Calcd. for $C_{19}H_{17}NO_3S_2$: C, 61.43; H, 4.61; N, 3.77. Found: C, 61.31; H, 4.48; N, 3.56.

4,12-Dihydrothieno[2',3':5,6][1,3]oxazepino[2,3-*a*]isoindol-10(5b*H*)-one (**13b**).

This product was isolated as white-yellow crystals after chromatography and recrystallization; mp 89-91° (ethanol/water); IR (KBr): ν 3010, 2951, and 1689 cm^{-1}; ^{1}H NMR: δ 4.42 (d, *J*=14.9 Hz, 1H, CH_2-O), 4.52 (d, *J*=16.4 Hz, 1H, CH_2-N), 4.64 (d, *J*= 14.9 Hz, 1H, CH_2-O), 5.47 (d, *J*=16.4 Hz, CH_2-N), 6.11 (s, 1H, O-CH-N), 6.67 (d, *J*=5.4 Hz, 1H, $H_{4\text{-thiophene}}$), 7.05 (d, *J*=5.4 Hz, 1H, $H_{5\text{-thiophene}}$), 7.49-7.61 (m, 3H, $H_{phthalimide}$), 7.79 (d, *J*=7.05 Hz, 1H, $H_{phthalimide}$); ^{13}C NMR: δ 38.9 (CH_2), 63.0 (CH_2), 89.7 (CH), 122.8 (CH), 123.0 (CH), 126.3 (CH), 129.8 (CH), 131.9 (CH), 132.1 (CH), 134.8 (C), 139.0 (C), 143.6 (C), 147.5 (C), 168.5 (C=O); MS (m/z) 257 (M^+).

Anal. Calcd. for $C_{14}H_{11}NO_2S$: C, 65.35; H, 4.31; N, 5.44. Found: C, 65.12; H, 4.27; N, 5.27.

Other Method for Preparation of 3-Arylmethyloxylactams (**12a,b**).

To a stirred solution under an atmosphere of dry argon α-hydroxylactam **11a** (or **11b**) (10 mmol) in 20 mL of dry THF at 0° was added by portions 0.48 g (12 mmol) of sodium hydride (60 % in mineral oil). After stirring for 30 min at room temperature, 10 mmol of benzyl chloride (or 3-bromomethylthiophene) dissolved in 25 mL of dry THF was added dropwise over a period of 10 min. The mixture was then allowed to react at the same

temperature for 24 h and carefully hydrolysed with cold water. The reaction mixture was extracted with dichloromethane and the organic layer was washed with water, brine, dried over magnesium sulfate and concentrated *in vacuo*. The resulting crude product was purified by recystallization (diethyl ether/hexane) or chromatography on silica gel column (dichoromethane/hexane, 4:1) to give **12a** (81 %) or **12b** (75 %) identical to 3-arylmethyl-oxylactams described above.

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REFERENCES AND NOTES

[1a] A. Wolpert, L. White, L. Dana, A. A. Sugerman, A. D. Arengo, G. M. Simpson, M. P. Bishop and D. M.; Gallant, *J. Clin. Pharmacol.*, **10**, 175 (1970); [b] J. Schmutz, *Arzneim. Forsch.*, **25**, 712 (1975).

[2] E. N. Greenblatt, A. S. Lippa and A. C. Osterberg, *Arch. Int. Pharmacodyn.*, **233**, 107 (1987).

[3] G. L. Sathananthan, R. Matz, H. Thompson and S. Gershon, *Curr. Ther. Res.*, **15**, 919 (1973).

[4] It has been reported also, by same authors, that Amoxapine appears to be devoid of anticholinergic or anticonvulsant activity. See: E. Greenblatt and A. C. Osterberg, *Fed. Proc*., **27**, 438 (1968).

[5] Y. Liao, B. J. Venhuis, N. Rodenhuis, W. Timmerman, H. Wikström, E. Meier, G. D. Bartoszyk, H. Böttcher, C. A. Seyfried and S. Sundell, *J. Med. Chem.*, **42**, 2235 (1999).

[6] K. Nagarajan, *J. Indian Chem. Soc.*, **74**, 831 (1997).

[7] A. R. Katritzky, Y-J. Xu, H-Y. He and S. Mehta, *J. Org. Chem.*, **66**, 5590 (2001) and the references cited therein.

[8] G. A. Kraus and S. Yue, *J. Org. Chem.*, **48**, 2936 (1983).

[9a] N. Yamazaki, H. Suzuki and C. Kibayashi, *J. Org. Chem.*, **62**, 8280 (1997); [b] N. Yamazaki, T. Ito and C. Kibayashi, *Synlett*, 37 (1999; [c] T. Ito, N. Yamazaki and C. Kibayashi, *Synlett*, 1506 (2001).

[10] R. Grigg, I. Köppen, M. Rasparini and V. Sridharan, *J. Chem. Soc., Chem. Commun.*, 964 (2001).

[11] Only one example of substituted pyrrolidino[1,3]oxazepine was obtained as a minor product (9.5% yield), see: J. Griffiths and J. A. Murphy, *Tetrahedron*, **48**, 5543 (1992).

[12a] A. Mamouni, A. Daïch, Š. Marchalín and B. Decroix, *Heterocycles*, **54**, 275 (2001); [b] X. Zhang, W. Jiang and A. C. Schmitt, *Tetrahedron Lett.*, **42**, 4943 (2001); [c] P. Pigeon, A. Mamouni, J. Sikoraiová, Š. Marchalín and B. Decroix, *Tetrahedron*, **57**, 4939 (2001); [d] J. Sikoraiová, Š. Marchalín, A. Daïch and B. Decroix, *Tetrahedron Lett.*, **43**, 4747 (2002).

[13a] N. Hucher, A. Daïch and B. Decroix, *Org. Lett.*, **2**, 1201 (2000); [b] N. Hucher, B. Decroix and A. Daïch, *J. Org. Chem.*, **66**, 4695 (2001); [c] A. Chihab-Eddine, A. Daïch, A. Jilale and B. Decroix, *Tetrahedron Lett.*, **42**, 573 (2001).

[14] N. Hucher, A. Daïch and B. Decroix, *J. Heterocyclic Chem.*, **35**, 1477 (1998).

[15a] H. E. Zaugg, *Synthesis*, 49 (1970); [b] H. E. Zaugg, *Synthesis*, 85 (1984); [c] H. E. Zaugg, *Synthesis*, 181 (1984); [d] The same *N*-acyliminium ion **B** was also generated from *N*-chloromethylphthalimide (**7**) in the presence of Brönsted or Lewis acid. For this end, see for example: [e] I. Iley, T. Calheiros and R. Moreira, *Bioorg. Med. Chem. Lett.*, **8**, 955 (1998), and [f] B. Venugopalan, P. J. Karnik and S. Shinde, *J. Chem. Soc., Perkin Trans. 1*, 1015 (1996), respectively.

[16] In this area, see for example: J. D. Coyle and G. L. Newport, *J. Chem. Soc., Perkin Trans. 1*, 93 (1980).

[17] S-D. Cho, H-J. Kim, C. Ahn, J. R. Falck and D-S. Shin, *Tetrahedron Lett.*, **40**, 3215 (1999).

[18] P. Pigeon and B. Decroix, *J. Heterocyclic Chem.*, **33**, 129 (1996).

[19] M. A. Pasquini, R. Le Goaller and J. L. Pierre, *Tetrahedron*, **36**, 1223 (1980).

[20] A. K. Rose, F. Greer and C. C. Price, *J. Org. Chem.*, **23**, 1335 (1958).

[21] A. Daïch, Š. Marchalín, P. Pigeon and B. Decroix, *Tetrahedron Lett.*, **39**, 9187 (1998).

[22] M. Wada, H. Nakai, K. Aoe, K. Kotera, Y. Sato, Y. Hatanaka and Y. Kanaoka, *Tetrahedron*, **39**, 1273 (1983).

[23] This product was prepared by heating at 90 °C in DMF *N*-bromomethylphthalimide and benzyl alcohol in near neutral conditions (92% yield); see: Y. Sato, H. Nakai, M. Wada, H. Ogiwara, T. Mizoguchi, Y. Migita, Y. Hatanaka and Y. Kanaoka, *Chem. Pharm. Bull*., **30**, 1639 (1982).

[24] The *N*-alkylated product **9a** was isolated from the mixture by chromatography on a silica gel column using a mixture of CH_2Cl_2/hexane (4:1) as eluent and its yield did not exceed 8% whatever the reaction conditions.

[25] When the reaction was performed at -40 to –35°, the reaction times increase to 2.5-3 days.

[26a] A. Mamouni, A. Daïch and B. Decroix, *J. Heterocyclic Chem.*, **33**, 1251 (1996); [b] J. Sikoraiová, A. Chihab-Eddine, Š. Marchalín and A. Daïch, *J. Heterocyclic Chem.*, **39**, 383 (2002).

[27] Acids other than PTSA and TFA provokes rapidly, in all cases, the decomposition of the starting α-hydroxylactams **11a,b**.

[28] A. Chihab-Eddine, A. Daïch, A. Jilale and B. Decroix, *J. Heterocyclic Chem.*, **37**, 1543 (2000).

[29] Diacetal products **12a** and **12b** were isolated, respectively, as white solid (mp=57-59° after recrystallization from diethyl ether/hexane) and uncoulorless oil.

[30] H. Ent, H. De Koning and W. N. Speckamp, *Heterocycles*, **30**, 501 (1990).