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General and Versatile Entry to 4,5-Fused Polycyclic Imidazolones Systems. Use of the Tandem Transposition/π-Cyclization of *N*-Acyliminium Species

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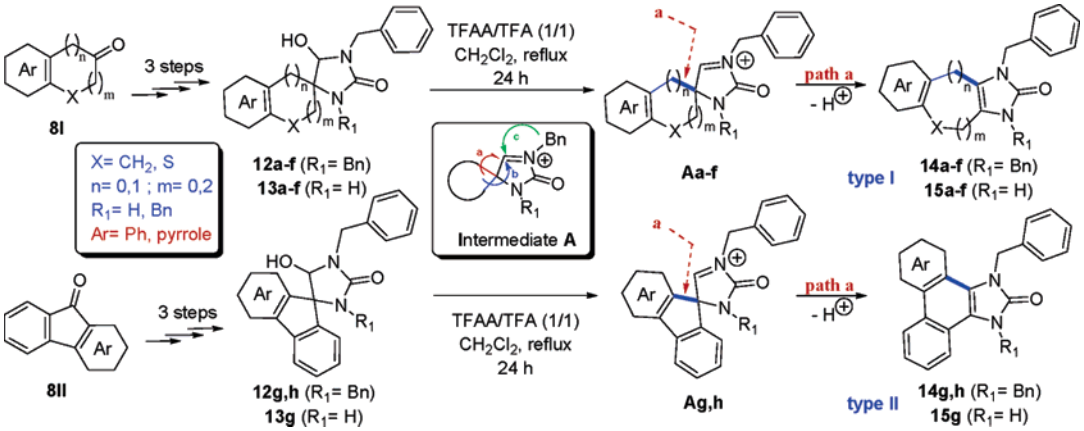

A simple and efficient methodology for the synthesis of 4,5-fused imidazolidin-2-ones from bicyclic and tricyclic ketones in a four-step sequence was described, by successive spirohydantoin Bucherer−Berg formation, mono- and dialkylation of the nitrogen atom of the hydantoin ring, regioselective reduction of one carbonyl function, and cationic cyclization associated with ring expansion. The key step of this sequential reaction was based on a tandem transposition/intramolecular amidoalkylation of cyclic spiro-*N*-acyliminium species. The process seems to be easy, general, regiospecific, resulted in the formation of polyheterocyclic systems containing an imidazolidin-2-one nucleus in good to excellent yields (67−99%), and is compatible with a large-scale production (up to 3 g of product **14**, for example). Also, this method allows the preparation of the novel heterocycles **14** and **15** that have pharmaceutically interesting profiles, which are not accessible through short current synthetic methods. Finally, products **15** bear a secondary amide function crucial for further transformations, including the introduction of various pharmacophore groups either at the C or the N atoms of the imidazole ring.

Introduction

Polysubstituted 4,5-diarylimidazoles are common heterocyclic components in biologically important small molecules, and consequently they constitute an interesting class of pharmaceuticals and investigational drugs.[1] During the past few years, they have received increasing attention, in the pharmaceutical industry and the medicinal chemistry community, due to their application in several major pathologies. As representative structures, *N*-substituted pyridin-4-yl-imidazole derivatives SB-235699 (**1a**),[2] SB-216995 (**1b**),[2] SB-203580 (**1c**),[4] SB-210313

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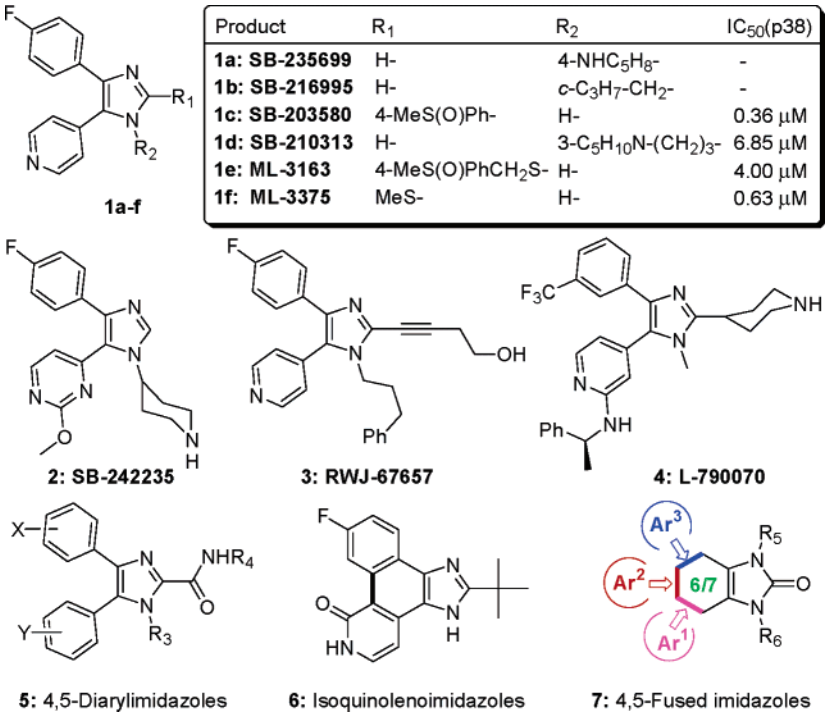

FIGURE 1. Inhibitors of p38α MAP kinase and cytokine release **1**−**4**, and inhibitors of other kinases **5**,**6** and our targets 4,5-fused polycyclic imidazoles **7**.

(**1d**),[5] ML-3163 (**1e**),[4] and ML-3375 (**1f**)[5] are potent and highly selective p38α MAP (mitogen activated protein) kinase inhibitors and involved in cytokine release.[2] Several other lead molecules (e.g., SB-242235 (**2**),[6] RWJ-67657 (**3**),[7] and L-790070 (**4**)[8]) have been advanced to proclinical and clinical studies. Interestingly, in the precedent year, two disclosures present scaffolds with structures related to the prototypical inhibitor (SB-203580 (**1c**)),[9] and structures of type **5**[10] containing replacements of the pyridine ring and substituents on the benzene and imidazole nucleuses have shown a distinct profile because they act as the native *Emieria tenella* cGMP-dependent protein kinases (PKGs) inhibitors in vitro, as anti-coccidial agents in chickens in vitro, and as anti-obesity agents, respectively. In the latter case, products **5** act as human CB1 (Cannabinoid receptor of type 1) receptor inverse agonist, which was implicated in both the energy balance and the control of weight via a dual mechanism of the regulation of energy expenditure and food intake modification.[11]

Interestingly, only one structure bearing all nucleuses present in the above prototype components (Figure 1) is mentioned in the literature. This product, as a pyridone-containing tetracycle **6** in which the pyridine and benzene rings are connected, inhibits efficaciously the Jak family of protein tyrosine kinase, which transduce extra-cellular signals by phosphorylating cytoplasmic proteins.[12]

The general synthesis of these kinds of products was built around substituted imidazole-2-thiones as the key intermediates followed by subsequent modification of the thioamide function via the corresponding 2-chloroimidazole using classical chemistry. These derivatives could be obtained using two different synthetic pathways starting from common ketones.

A first general method was based on the construction of imidazol-2-ones according to the Lettau procedure[13] using the ''ketone→nitrosation into α-hydroxyiminoketone→cyclization" strategy. Because this protocol has been initially limited to the synthesis of monosubstituted imidazole with a simple alkyl substituent at the C_4- or C_5-position of the imidazole ring, serious modifications in the reaction conditions were introduced by

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Laufer et al.,[4] and consequently the sequence resulted in the formation of 4,5-diarylimidazol-2-ones bearing a wide range of different substituents at N_1.

A second general method also used that strategy, but the latter step furnished imidazole-*N*-oxides components. The latter step constitutes a limitation of the sequence because the expected imidazole-*N*-oxides derivatives could not be synthesized under acidic conditions. However, this reaction becomes effective under neutral conditions with good yields when sophisticated and expensive thiazinanes were used as partners of the reaction. In an ultimate stage, *N*-oxides products were converted successfully and efficaciously into corresponding imidazole-2-thiones with carbocyclic 1,3-dithiones.[3−5] These cyclic thiones, which were required for the preparation of 2-alkylsulfanylimidazoles as **1c**, **1e**, and **1f**, could be obtained also directly when α-oximoketones were reduced selectively into α-aminoketones prior to the ring closure with potassium thiocyanate.[14] More recently, other variations using α-hydroxyketones protected at the OH function[9] or not,[10] α-bromoketones[9] and diketones[9] leading, respectively, to 2-piperidinoimidazoles as **4** and 2-carboxamidoimidazoles as **5**, were also developed. Finally, an additional multicomponent route to 2,4,5-triarylimidazoles kinase inhibitors was described in two steps by reaction of α-hydroxyiminoketones, aldehydes, and ammonium acetate in refluxing acetic acid followed by the Lewis acid induced *N*-hydroxyimidazole N−O cleavage.[12,15] Also, this approach was demonstrated to be effective in one pot and two steps under microwave assistance,[16] showing evidence of the thermally N−O linkage breaking. By using the photochemistry of 2-pyridone readily accessible from 2-alkyl-4,5-diarylimidazoles, the oxidative cyclization of the latter into the pyridone-containing tetracycle[12] constitutes a valuable method to accede new generation of products **6**, which have new spectra of kinase activities.

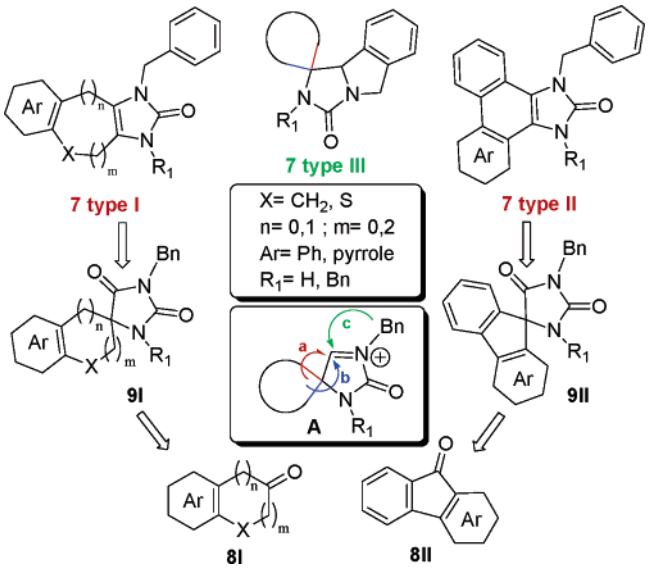
Results and Discussion

Because the synthetic approaches toward these types of fused imidazoles[17] are few explored in the literature, allied with our interest in the development of synthetic methodologies toward original aza-heterocyclic systems containing an imidazole ring fused to polycyclic skeletons with promising pharmaceutical properties, we have continued to explore synthetic opportunities on the basis of our recent reports using *N*-acyliminium cyclization in tandem with Grignard reaction,[18] Pummerer cyclization,[19] *N*-acyliminium ion isomerization,[20] and *N*-acyliminium ion isomerization/double alkyl transposition.[21]

To the best of our knowledge, the application of this π-cationic cyclization in association with alkyl, aralkyl, and aryl transposition, which would produce the central six- and seven-membered systems as fused imidazole compounds of types **I** and **II** (Scheme 1), represents a novel and easy illustration of this chemistry. In fact, as highlighted in the retrosynthetic scheme, the selection of different alkyl, aralkyl, and aryl substituents in spirohydantoin systems at the angular carbon as in **9I** and **9II**, which are accessible from ketones **8I** and **8II**, allows consideration of the stable *N*-acyliminium cation **A**. This would act as an alkyl, aralkyl, and/or aryl scavenger after their transposition according to pathways **a** and **b** in Scheme 1. Also, the direct π-cyclization process leading to products **7** of type **III**, with benzene as internal nucleophile, could constitute a serious competing reaction. In the requisite intermediate **A** generated from α-hydroxy lactams in acidic medium, cyclization into imidazoles **7** (types **I** and **II**) and/or their regional isomers not represented in the scheme may indeed originate from intramolecular attack of either the electron-rich migrating fragment or the less rich migrating one. At this stage, the measurement of the impact of the nature of the migrating fragment constitutes an important and interesting challenge for the comprehension of the scope and limitation of this process. In this sense, we present herein the preliminary results of our finding on this combination of transposition/π-cationic cyclization and a mechanistic aspect of the transformation to access a library of small molecules containing an imidazole nucleus fused to simple and complex carbocycles and heterocycles.

For our study, spirohydantoins **9** as starting materials were synthesized (Scheme 2). For this purpose, we have chosen the use of the well-established Bucherer−Berg reaction[22] for the following reasons: (1) the reaction uses cheap reagents as well

SCHEME 1. Retrosynthetic Scheme Leading to Our Targets 4,5-Fused Polycyclic Imidazoles 7 of Types I, II, and III from Bicyclic Ketones 8I and Tricyclic Ketones 8II[a]



[a] Key: Only cyclized products **7** of types **I**, **II**, and **III**, as possible regioisomers, are represented.

(14) Interestingly, the concomitant reduction of the ketone adjacent to the oxime has been rendered marginal when the reduction process was performed with Pd-catalyzed hydrogenolysis under acid conditions. For this end, see: Laufer, S. A.; Wagner, G. K.; Kotschenreuther, D. A.; Albrecht, W. *J. Med. Chem.* **2003**, *46*, 3230−3244.

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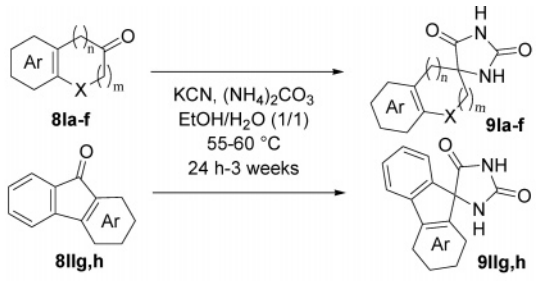
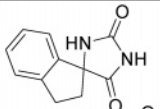
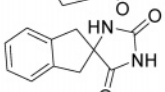
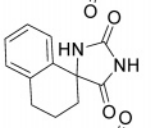
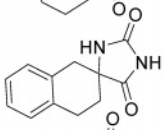
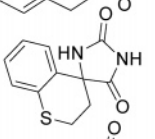
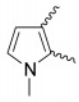
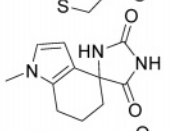
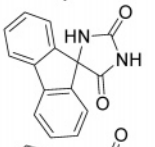
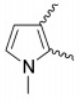
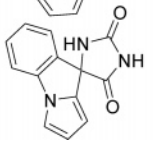
SCHEME 2. Scheme Leading to Starting Spirohydantoins 9Ia−f and 9IIg,h[a]



Product	n	m	Ar	X	Spirohydantoin	Yield (%)
9Ia	0	1	Ph	CH_2		82[a]
9Ib	1	0	Ph	CH_2		63[a]
9Ic	0	2	Ph	CH_2		76[a]
9Id	1	1	Ph	CH_2		97[b]
9Ie	0	2	Ph	S		98[a]
9If	0	2		CH_2		21
9IIg	-	-	Ph	-		88[c]
9IIh	-	-		-		12

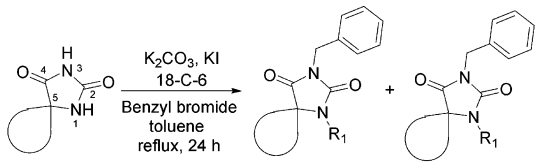
[a] Key: For comparisons, see the following references: (a) ref 23; (b) ref 39; and (c) ref 22b.

as soft conditions, (2) the reaction was accomplished in one step starting from the appropriate ketones, and finally (3) the reaction is easy to use and is compatible with a large-scale production. Under these conditions (i.e., 1.5 equiv of KCN, 10 equiv of $(NH_4)_2CO_3$, EtOH−H_2O (1:1), 55−60 °C), good to excellent yields (63−98%)[23] were obtained after 24 h to 3 weeks of reaction with ketones **8Ia−e** and **8IIg**. A substrate in pyrrole series as **8If**[24] and **8IIh**[25] underwent spirocyclization in very poor yields of 12% and 21%, respectively. It is noteworthy that, although a variety of reaction times, solvent ratios, and temperatures were explored, the formation of spiro-hydantoins **9If** and **9IIh** was not accompanied by the increase of the yield. This is probably due to the relatively low electrophilicity of ketones as well as their low solubility in the solvents of the reaction (EtOH−H_2O). The structure of spirohydantoins **9** was secured by their ^1H and ^{13}C NMR spectra, including DEPT programs and elemental analyses. The ^1H NMR spectra showed two NH singlets exchangeable with D_2O. More interestingly, the ^{13}C NMR spectra revealed the presence of two quaternary carbons corresponding to C_2═O and C_4═O hydantoin functions at δ = 156.5−156.9 ppm and δ = 173.6−178.6 ppm, respectively. The spectra revealed also a ''spiro-carbon" C_4 at δ = 60.8−71.9 ppm. These values are comparable to that reported in the literature for related spirohydantoins.[22,23]

Next, we treated the spirohydantoins **9** with base and halides in different exploratory experimental N-alkylation conditions. From these results, its seems that the alkylation process under solid−liquid−phase transport catalysis (PTC) conditions constitutes the best method to accomplish this sequence because they furnish two separable products in accordance with our prediction. The monoalkylation reaction of hydantoin **9** at N_3 exclusively could also be achieved in acceptable yield by using KOH as a base and polar protic (EtOH) or polar nonprotic (DMSO) as solvent according to the reported protocols.[26] The monoalkylation process of hydantoin was also reported in the literature by using the Mitsunobu synthesis.[27]

So, as depicted in Scheme 3, the N_1,N_3-dialkylated and N_3-alkylated spirohydantoins **10a−h** and **11a−g** were obtained by condensation of benzyl bromide with spirohydantoins **9a−h** under PTC using anhydrous potassium carbonate as base and a mixture of potassium iodide and crown ether 18-C-6 as

SCHEME 3. Scheme Leading to N_1,N_3- and N_3-Alkylated Spirohydantoins 10a−h and 11a−g[a]



Product	R_1	Yield (%)	Product	R_1	Yield (%)
10a	Bn	16	**11a**	H	63
10b	Bn	35	**11b**	H	29
10c	Bn	21	**11c**	H	57
10d	Bn	26	**11d**	H	37
10e	Bn	36	**11e**	H	25
10f	Bn	26	**11f**	H	48
10g	Bn	30	**11g**	H	39
10h	Bn	39	**11h**	H	-[a]

[a] Key: N_1-Benzylation reaction was not observed in this case.

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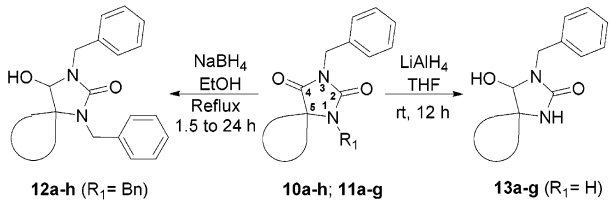
SCHEME 4. Scheme Leading to α-Hydroxyspirolactams 12a−h and 13a−g[a]



12a-h (R_1= Bn) **10a-h**; **11a-g** **13a-g** (R_1= H)

Product	R_1	Yield (%)	Product	R_1	Yield (%)
12a	Bn	92[a,b]	**13a**	H	74[a]
12b	Bn	91	**13b**	H	85[a]
12c	Bn	97[b]	**13c**	H	86[a,b]
12d	Bn	99[a]	**13d**	H	71[a]
12e	Bn	97	**13e**	H	97
12f	Bn	99	**13f**	H	96[c]
12g	Bn	96	**13g**	H	98[d]
12h	Bn	86[a,b]	**13h**	H	-[e]

[a] Key: (a) Yields of the crude product. (b) The products were obtained as two inseparable isomers. (c) The product is not isolated in pure form. (d) This hydroxyspirohydantoin was isolated in ethoxy form. (e) No reduction was conducted in this case.

catalysts.[28] Under these conditions, compounds **10a−h** and **11a−g** as crystalline solids were obtained after refluxing in dry toluene for 24 h, followed by chromatography separation on a silica gel column in yields ranging from 13% to 39% for **10a−h** and 25% to 57% for **11a−g**, respectively. From these results, it is clear that the N_1,N_3-dialkylated spirohydantoins are the major products except for spirohydrantoins **10b** and **10e**. Also, from **9h** as a starting spirohydrantoin, only the dialkylated product **10h** was isolated as the sole reaction product with, however, a modest yield (39%).

The alkylated spirohydantoins **10** and **11** were then submitted separately to the reduction reaction, for the isolation of the corresponding α-hydroxyspirolactams as *N*-acyliminium cations precursors (Scheme 4). According to Hough et al. reports on hydantoins,[29] inspired from the Speckamp work on N-alkylated succinimides,[30] the reduction of N_1,N_3-dialkylated spirohydantoins **10a−h** was carried out with a large excess of $NaBH_4$ (6 equiv) in dry ethanol at reflux for 1.5−24 h (the reaction was monitored by TLC using a silica gel column and CH_2Cl_2 as eluent). The resulting α-hydroxyspirolactams **12a−h** were isolated in pure form after classical workup followed by recrystallization from suitable solvent in excellent yields (86−99%), although mixtures of isomers were often obtained. In fact, 4-hydroxy-N_1,N_3-dibenzylspirohydantoins **12b**, **12e**, and **12g** were isolated in yields of 91%, 97%, and 96%, respectively, as the sole reaction products. On the contrary, 4-hydroxyspirohydantoin derivatives **12a**, **12d**, **12f**, and **12h** were obtained in 9:1, 5.5:4.5, 9.5:0.5, and 7:3 mixtures of two isomers inseparable in yields of 92%, 99%, 99%, and 86%, respectively. Finally, in the case of component **12c**, only traces of the second isomer were observed.

With the same protocol as above, the reduction of N_3-benzylated spirohydantoin **11a**, as a representative model of monoalkylated spirohydantoins class, occurred and led to the expected α-hydroxyspirolactam **13a** as a minor and inseparable reduced isomer. This was accompanied, particularly, with the opened ureine-alcohol and other products difficult to identify. The use of this protocol at ambient temperature led also to starting material unchanged due to its insolubility in ethanol **11a**. To perform this sequence, our attention was directed to other reductant agents. Earlier studies have shown that *N*$_3$-alkyl- and *N*$_3$-aralkylhydantoins substituted at C_3 could be reduced selectively into corresponding 4-hydroxyimidazolidin-2-ones with $LiAlH_4$ in anhydrous THF or diethyl ether at room temperature.[26b,c,29b,31] The reaction under slightly more vigorous conditions (reflux of THF or diethyl ether) gave the expected products accompanied by imidazolidin-2-ones,[32] imidazoles,[33] and/or imidazolidines.[32,33] In light of these findings, we decided to adopt this protocol for the above spirohydantoins. At the outset, spirohydantoin **11a** was engaged in this reaction. Surprisingly, this yielded cleanly α-hydroxyspirolactam **13a** as a >9.5:0.5 mixture of two diastereomers in 74% yield after treatment of **11a** with 3 equiv of $LiAlH_4$ in dry THF at −5 to 0 °C for 1 h, and then 12 h at ambient temperature. Recrystallization of the crude product from dry ethanol led to **13a** in pure form.

The results with a variety of *N*$_3$-benzylspirohydantoins **11b−g** are presented in Scheme 4 and showed the effectiveness in all cases of the experimental procedure that was characterized, in addition, by operational simplicity. Because byproducts as spiroimidazolidin-2-ones[32] and/or spiroimidazolidines[32,33] are formed according to the reports of the above authors[26,29] and others[32,33] for "nonspiranic" hydantoins, isolation of the expected products **13b−g** entailed simply diluting the reaction mixture with EtOH−5% HCl solution followed by filtration on a short column of Celite, concentration, water dilution, organic separation, solvent evaporation, and finally recrystallization of the crude products. In some cases, prior removal of the organic solvent facilitated this process. The crude products isolated in this fashion precipitate out of the solution and were generally of high purity as judged by NMR spectral data and elemental analyses (products **13a−d** and **13g**). From the results summarized in Scheme 4, it is apparent that high to excellent yields of α-hydroxyspirolactams **13** are generally obtained except in the case of products **13a** and **13d**, for which yields are of 74% and 71%, respectively. Interestingly, adducts **13a**, **13b**, **13d**, and **13g** were obtained as a single isomer. Component **13g** was isolated in ethoxy form, which resulted from the etherification of its α-hydroxyspirolactam congener with ethanol in acidic medium via the intermediacy of *N*-acyliminium cation.[30] In addition, if α-hydroxyspirolactam **13c** was isolated as a mixture of two isomers with, however, only trace amounts of the minor one, α-hydroxyspirolactams **13e** and **13f** were obtained in 9.5:0.5 and 5.5:4.5 ratios and as inseparable mixtures.

One final aspect that deserves comment concerns the structure determination of α-hydroxyspirolactams **12a−h** and **13a−g**.

(28) (a) Hucher, N.; Daïch, A.; Decroix, B. *J. Heterocycl. Chem*. **1998**, *35*, 1477−1548. (b) Chihab-Eddine, A.; Daïch, A.; Jilale, A.; Decroix, B. *J. Heterocycl. Chem*. **2000**, *37*, 1543−1548.

(29) Hough, T. L. *J. Heterocycl. Chem*. **1989**, *26*, 1523−1525. See also: Cortes, S.; Kohn, H. *J. Org. Chem*. **1983**, *48*, 2246−2254.

(30) Speckamp, W. N.; Moolenaar, M. J. *Tetrahedron* **2000**, *56*, 3817−3856.

(31) Marquez, V. E.; Twanmoh, L.; Wood, H. B.; Driscoll, J. S. *J. Org. Chem*. **1972**, *37*, 2558−2561.

(32) (a) Marshall, F. J. *J. Am. Chem. Soc*. **1956**, *78*, 3696−3697. (b) De la Costa, E.; Ballestros, P.; Trigo, G. G. *Heterocycles* **1981**, *16*, 1647−1650.

(33) Wilk, I. J.; Close, W. *J. Org. Chem*. **1950**, *15*, 1020−1022.

Thus, the assignment of these structures was made on the basis of their IR and NMR spectra (^1H,^{13}C experiments including NOE difference and DEPT programs, respectively). In the case of solids, their elemental analyses were also performed. So, the ^1H NMR spectra of **12a**−**h** ($CDCl_3$) and **13a**−**g** (DMSO-d_6) showed the methylene group of the −N−CH_2− functionalities as an AB system due to the diastereotopic effect with a coupling constant of $J = 15-17$ Hz for **12a**−**h** and **13a**−**g** characteristic of *gem* protons. Also, the newly created angular proton CH in **12a**−**h** appears as a doublet at $\delta = 4.47-4.89$ ppm with a coupling constant of $J = 7-11$ Hz characteristic of a geminate coupling between CH and OH in the secondary "alcohol" function,[34] except for α-hydroxyspirolactam **12f** in which no coupling of CH(OH) was observed. Interestingly, the same angular protons in **13a**−**g** appear as a singlet in the majority of the cases at $\delta = 4.31-4.70$ ppm except for **13c**. In this case, CH appears as a doublet at $\delta = 4.71$ ppm with $J = 10$ Hz comparable to that observed for its homologues **12a**−**h**. In addition, the ^1H NMR spectral data of **13a**−**g** showed an N−H signal as a broad singlet at $\delta = 4.69-7.10$ ppm, which is exchangeable with D_2O. Likewise, the key feature in the ^{13}C NMR spectra of 4-hydroxyspirohydantoins **12a**−**h** and **13a**−**g** was the appearance of an additional tertiary carbon (CH(OH)) at $\delta = 82.4-86.6$ ppm for **12a**−**h** and at $\delta = 84.4-85.8$ ppm for **13a**−**g**, while, in comparison to their spirohydantoins congeners **10a**−**h** and **11a**−**g**, one quaternary carbon ($\delta_{C=O} = 170.9-175.9$ ppm for **10a**−**h** and $\delta_{C=O} = 172.0-176.4$ ppm for **11a**−**g**) disappears in the aromatic region. These facts are the consequence of the regioselective reduction of one of the carbonyl functions under the conditions discussed above. Importantly, from an examination of the above results, it is apparent that the stereochemical outcome of the reduction reaction is independent of the substitution at nitrogen(s) atom(s) as well as the "spiro" fragment attached at the C_4 position of the hydantoin nucleus. Interestingly, these facts were of no consequence to the overall synthetic strategy because the hydroxyspirolactams furnished under acidic influence a planar *N*-acyliminium species as intermediates of the cyclization reaction.

Because of the small body of literature on hydroxycyclanespirolactams regarding the reactivity of these functionalities in acidic medium[35] allied with the fact that only N_3-aralkyl-(alkenyl and acetylenic)-4-hydroxyimidazolidin-2-ones[26a−c,36] and 4-alkenyl-4-hydroxyimidazolidin-2-ones[37] were explored in intramolecular *N*-carbamoyliminium ion cyclization reactions, the behavior of *ω*-carbinollactams of types **12** and **13** bearing two nucleophiles was examined under acid influence. The hydantoins in substrates **12** and **13** differed in the nature of the cycle as "spiro" group attached at the C_5 position, and minor variation also existed at the N_1 position ($R_1 \simeq$ Bn for **12** and $R_1 \simeq$ H for **13**).

At the outset of our investigations, the 4-hydroxyimidazolidin-2-ones **12a** ($R_1 \simeq$ Bn) and **13a** ($R_1 \simeq$ H) were chosen as test examples for this intramolecular amidoalkylation transformation (Scheme 5). Thus, treatment of the *N*-acyliminium precursor **12a** with neat TFA,[36a] formic acid,[26b,37] catalytic amounts of PTSA,[26a,35a−c] or TFAA alone[26c] or in the presence of Lewis acid as $SnCl_4$[26b] failed or furnished a mixture of some products accompanied in all cases by the unreacted starting material. The best formulation to accomplish this reaction totally seems to be a mixture of TFAA/TFA in precise proportion (1/1) as mentioned in a few cases earlier.[26a,b] In these acidic conditions (i.e., TFAA/TFA (1/1) with a slight excess (1.3 equiv) of each reactant relative to substrate, CH_2Cl_2, reflux, 24 h), the cyclized product, identified as 1,3-dibenzyl-4,5-dihydrobenzo[*e*]benzimidazol-2-one (**14a**), was isolated as a crystalline material in 97% yield. From this result, its seems that the reaction did not occur by direct attack of the *N*-acyliminium intermediate **Ia** (Scheme 5) with the *π*-aromatic system by N_3 to furnish the spiro-fused imidazolone product of type **III** (Scheme 1), but by a tandem transposition/cationic cyclization process in a one-pot procedure. To determine the nature of the fragment, which transposed during the process, the examination of the "pseudounsymmetrically" *ω*-carbinollactam **13a** was necessary. So, **13a** under the same protocol as above led to 1-benzyl-4,5-dihydrobenzo[*e*]benzimidazol-2(3*H*)-one (**15a**) in 92% yield after recrystallization of the crude product from dry ethanol. The phenyl migrating group during the reaction as well as the structures of the cyclized products **14a** and **15a** were determined from a consideration of the published results in related bicyclic imidazolones.[35] Confirmation was obtained from NOE experiments that involved irradiation of the methylene protons of the benzyl group and aromatic proton H_9 of the monobenzylated cyclized product **15a** (see Scheme 5). In this case, the resulting NMR spectra exhibited a significant NOE enhancement, indicating that the H_9 and the methylene protons are spatially proximate and consequently the migrating group is on the same side of the benzyl group. Finally, because of the potential concurrent NOE effects in the same spectral region of the two benzylic protons, the NOE experiments were not done on the product **14a**.

Having established the facility and capacity of "symmetrical" and "unsymmetrical" hydroxylactams **12a** and **13a** to provide a tandem aryl transposition/*π*-cationic cyclization in forming interesting fused *N*-heterocyclic systems, we envisioned whether this process might be extended for the preparation of other six-membered rings, corresponding seven-membered rings bearing a heteroatom or not, and other aromatic nuclei fused to imidazolone. Thus, attempts under our cyclization protocol as delineated in Scheme 5 from hydroxylactams as **12b**−**e** and **13b**−**e** proved successful in all cases, and in each case only one product was obtained with excellent yields ranging from 86% to 98% except for product **14b**. In the latter case, the 1,3-dibenzyl-4,9-dihydrobenzo[*f*]benzimidazol-2-one (**14b**) (38%) was accompanied by the corresponding oxidized component, 1,3-dibenzylbenzo[*f*]benzimidazol-2-one (**18**), in 58% yield and was easily separated by chromatography on a silica gel column using a mixture of cyclohexane/AcOEt in a 3/2 ratio as eluent. Also, in the case of substrate **13d**, no reaction occurred; only trace amounts of starting material were recovered. From these results, products **14a**,**c**,**e** and **15a**,**c**,**e** showed an aryl migrating group, while products **14b**,**d** and **15b** evidenced the migration of the benzyl group instead of the phenylethyl one for **14d**. Importantly, in all cases, the reaction seems to be regiospecific because during the cyclization process only the

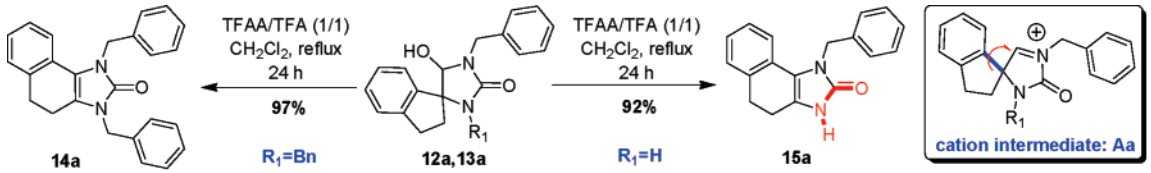
(34) Comparable coupling constant values are traditionally observed in the α-hydroxylactams products. This phenomenon is breakable when adding D_2O. See refs 18−21 for examples.

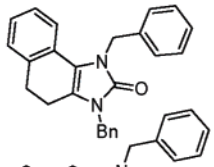
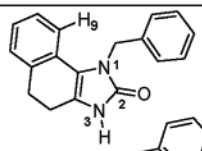
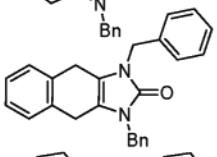
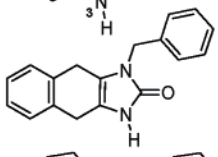
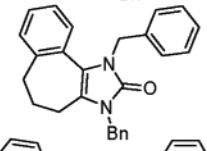
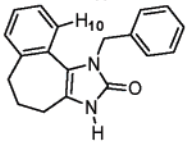
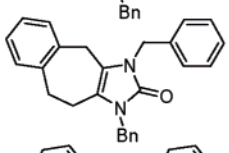
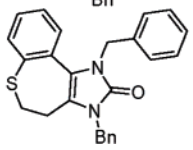
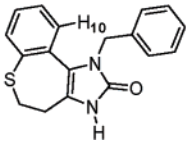
(35) To our knowledge, only a few reports in this area are published. See: (a) Rubido, J.; Pedregal, C.; Espada, M. *Synthesis* **1985**, 307−309. (b) Salazar, L.; Rubido, J.; Espada, M.; Pedregal, C.; Trigo, G. *J. Heterocycl. Chem.* **1986**, *23*, 481−485. (c) Pedregal, C.; Espada, M.; Salazar, L. *J. Heterocycl. Chem.* **1986**, *23*, 487−489.

(36) (a) Kano, S.; Yuasa, Y.; Yokomatsu, T.; Shibuya, S. *Synthesis* **1983**, 585−587. (b) Hamersma, J. A. M.; Nossin, P. M. M.; Speckamp, W. N. *Tetrahedron* **1985**, *41*, 1999−2005.

(37) Liao, Z.-K.; Kohn, H. *J. Org. Chem.* **1985**, *50*, 1884−1888.

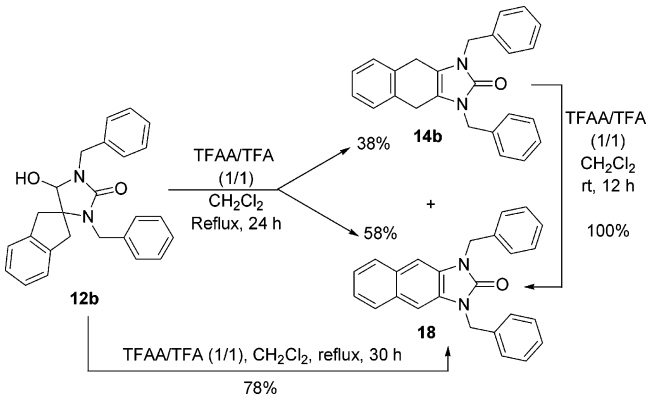
SCHEME 5. Synthetic Pathway Leading to 4,5-Fused Imidazolidin-2-ones 14 and 15[a]



N°	n	m	Ar	X	Isolated imidazolone **14a-e** (R_1= Bn)	Yield (%)	Isolated imidazolone **15a-e** (R_1= H)	Yield (%)
12a,13a	0	1	Ph	CH_2		97		92
12b,13b	1	0	Ph	CH_2		38[a]		88
12c,13c	0	2	Ph	CH_2		94		98
12d,13d	1	1	Ph	CH_2		89	-	-[b]
12e,13e	0	2	Ph	S		86		92

[a] Key: (a) This product was accompanied by the oxidized cyclic component **18** in 58% yield. (b) No tandem transposition/cyclization was observed in this case.

SCHEME 6. Synthetic Transformations of Hydroxy Lactam 12b to 1,3-Dibenzyl-4,9-dihydrobenzo[*f*]benzimidazol-2-one (14b) and 1,3-Dibenzylbenzo[*f*]benzimidazol-2-one (18)



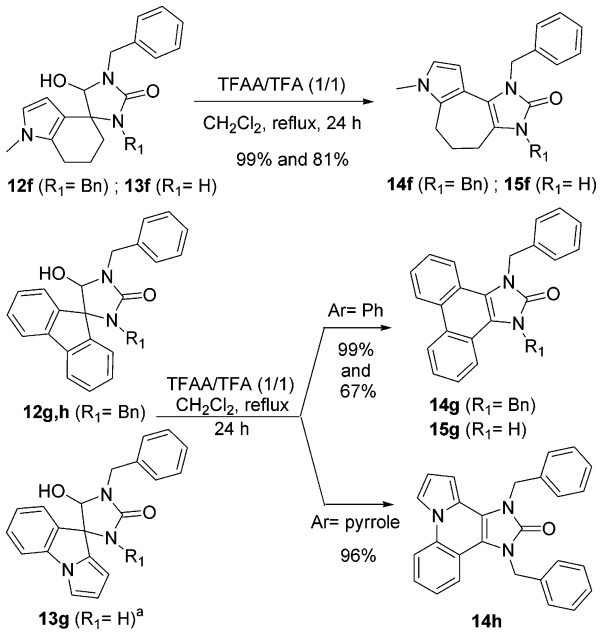
transposition of the electronically rich group was taken into consideration.

Taking into account that product **14b** is unstable under the conditions of the reaction, an additional study on the transposition/N-amidoalkylation of **12b** was envisaged. So, as highlighted in Scheme 6, exposure of the isolated product **14b** to the well-established protocol gave after 12 h of the reaction exclusively the oxidized product **18** in quantitative yield. No additional purification of the product was needed. Because of the facility of this oxidation reaction, which did not need any activator, and due to the good acidity of the methylene protons in the 4,9-dihydrobenzo[*f*]benzimidazol-2-one core of **14b**, product **18** was also obtained directly from hydroxyspirolactam **12b** in 78% yield after chromatography purification followed by recrystallization from ethanol/diethyl ether. Also, in this case, we have used the same general protocol established above, but 30 h at refluxing CH_2Cl_2 was necessary for complete reaction (monitored by TLC using cyclohexane/AcOEt (3/2) as eluting solvents).

To establish the generality and versatility of this tandem cyclization process, we decided to study the effect of heterocyclic, tricyclic, and triheterocyclic nuclei as tetrahydroindole, fluorene, and pyrrolo[1,2-*a*]indole. At the same time, our interest was also to measure the impact of the steric and electronic effects on the transposition-cyclization step.

Thus, the hydroxy lactams **12f** and **13f** in the tetrahydroindole series were treated with TFAA/TFA (1/1) according to the established protocol given above. The examination of the TLC of the reaction mixture indicated the presence of only one product (Scheme 7), which, after a classical workup, was identified as **14f** and **15f**, respectively, resulting from the successive formation of *N*-acyliminiun cation intermediate **Af** (Scheme 1), the transposition of the pyrrole ring, and deprotonation. This process occurs cleanly and affords the 4,5-fused imidazol-2-ones **14f** and **15f** in 99% and 81% yields, respec-

SCHEME 7. Synthetic Transformation of Hydroxyspirolactams 12f−h and 13f,g into Azatricyclic and Azatetracyclic Systems Containing an Imidazol-2-one Nucleus[a]



[a] Key: This hydroxyspirolactam **13g** was isolated in ethoxy form.

tively. Although the pyrrole nucleus is present instead of the phenyl one (in the *N*-acyliminium cations precursors **12a**,**c**,**e** and **13a**,**c**,**e**), there is no discernible preference between the phenyl and pyrrole groups. Furthermore, the pyrrole ring seems to be stable in the TFAA−TFA combination without notable affection of the transformation yields.

Similarly as above, hydroxyspirolactams in fluorene series **12g** and **13g** led to the cyclized products **14g** and **15g**. In this reaction, the starting *N*-acyliminium ion precursor **13g** was in the ethoxy form (hydroxy- and ethoxylactams generate the same *N*-acyliminium species in acidic medium). If the "symmetrically" imidazol-2-one product **14g** was isolated in an excellent yield of 99%, the "unsymmetrically" imidazol-2-one **15g** was isolated in a decreased yield of 67%. This effect has also been observed as above for the "pseudounsymmetrically" imidazol-2-one **15f** (81%) as compared to its "pseudosymmetrically" homologue **14f** (99%). Furthermore, the change of the steric effect by considering hydroxyspirolactam in pyrrolo[1,2-*a*]indole series did not affect the course of the reaction because the treatment of **12h** led to the cyclized product **14h** in a very good yield of 96%.

The synthetic pathway leading to the cyclized products **14a**−**f** and **15a**−**f** occurred through a cascade process and commences with the formation of *N*-acyliminium species **Aa**−**f** in acid conditions. At this stage, two pathways **a** and **b** were possible (Scheme 8). The first pathway **a** consists of the heterolytic cleavage of the linkage Aryl−$C_{spiranic}$ ($n = 0$). The transposition of the resulting electronically rich group (phenyl or pyrrole ring in the case of **14a**,**c**,**e**,**f** and **15a**,**c**,**e**,**f**) to form the cyclic *N*-acyliminium cations **Ba**−**f** was followed in an ultimate step by its spontaneous deprotonation, affording the polyheterocyclic targets **14a**−**f** and **15a**−**f**. Also, when the *n* value differs from 0, only the rich group migrates preferentially (benzyl group in the case of **14b**,**d** and **15b**). Finally, the formation of the products **14g**,**h** and **15g** seems to pursue the same facts because, in these cases, no preference between the migrating groups could be done. In fact, in **14g** and **15g** only one phenyl migrating group exists, while in **14h** the presence of the benzyl group attached at N_1 and N_3 rendered the choice of the migrating group inoperative. These suggestions were based on published results[35] and on our own studies using ^{1}H NMR consideration as detailed above. As a consequence, the second pathway **b** consisting of the formation of the polyheterocyclic systems **16a**−**f** and **17a**−**f** was definitely excluded.

Several key features in the ^{1}H and ^{13}C NMR spectra of the cyclized compounds **14a**−**h** and **15a**−**g** were diagnostic of structure. For instance, in the ^{1}H NMR spectra of 1,3-dibenzylimidazolidin-2-ones **14a**−**h**, the methylene protons of the −N−CH_2− functionalities, which were an AB system in hydroxylactams congeners **12a**−**h**, appeared as a distinct singlet between $\delta = 4.81$ and 5.70 ppm due to the absence of the diastereotopic effect. The spectra showed also the disappearance of two peak signals corresponding to the angular proton at C_4 and OH (CH(OH) coupling) in **12a**−**h**. For 3-benzylimidazolidin-2-ones **15a**−**g**, the ^{1}H NMR spectra revealed the presence of a distinct N−H absorption at $\delta = 9.76-10.68$ ppm for **15a**−**f** and in the aromatic region between $\delta = 7.28$ and 7.72 ppm for product **15g**, which disappeared after D_2O exchange. They revealed also the presence of a singlet corresponding to the methylene protons of the benzyl group. Of particular note, this one appeared at $\delta = 4.48$ and 5.66 ppm and was in general upfield as compared to those in the structures of **14a**−**h**. A small shielding of $\Delta\delta = 0.10-0.18$ ppm between products **14** and **15** was observed in all cases except for **14e** and **15e** in which it was $\Delta\delta = 0.50$ ppm.

Carbon-13 NMR data proved to be of particular value in the assignment of the structure of 1,3-dibenzylimidazolidin-2-ones **14a**−**h** and 3-benzylimidazolidin-2-ones **15a**−**g**. The most distinguishing feature in the ^{13}C NMR spectra was the regular appearance of one downfield signal between $\delta = 153.3$ and 156.0 ppm for **14a**−**h** and $\delta = 153.9$ and 156.2 ppm for **15a**−**g**, which have been attributed to the carbon C_2.[38] Variation of the "substituents" at C_4 and C_5 positions on the imidazolidin-2-one ring led to only small changes in the chemical shifts values for this resonance. Yet we noted in this data set for the same carbon C_2 a consistent upfield shift of $\Delta\delta = 0.90-1.20$ ppm in comparison between **14a**−**e** and **15a**−**e**, while when we are considering products **14f**−**h** and **15f**,**g**, importantly, a small downfield signal of $\Delta\delta = 0.50-0.80$ ppm was observed. This is due probably, in the latter cases, to the presence of diheterocyclic, tricyclic, and triheterocyclic fused imidazolidin-2-one as constraint systems.

In summary, N_1,N_3-dibenzyl- and N_3-benzylspirohydantoins **10a**−**h** and **11a**−**g**, obtained easily in good yields by the N-alkylation process under PTC conditions in one step from corresponding spirohydantoins **9Ia**−**f** and **9IIg**,**h**, have been shown to undergo $NaBH_4$ reduction (EtOH, reflux, 1.5−24 h) and $LiAlH_4$ reduction (THF, rt, 12 h) to give, respectively, N_1,N_3-dibenzyl-4-hydroxy-5-spiroimidazolidin-2-ones (**12a**−**h**) and N_3-benzyl-4-hydroxy-5-spiroimidazolidin-2-ones (**13a**−**g**) in good to excellent yields. It is noteworthy that the use of $LiAlH_4$ or $NaBH_4$ for reduction of spirohydantoins **10a**−**h** or

(38) (a) Fujiwara, H.; Bose, A. K.; Manhas, M. S.; Van der Veen, J. M. *J. Chem. Soc., Perkin Trans. 2* **1980**, *11*, 1573−1577. (b) Poupaert, J. H.; Claesen, M.; Degelaen, J.; Dumont, P.; Toppet, S. *Bull. Soc. Chim. Belg.* **1977**, *86*, 465−472.

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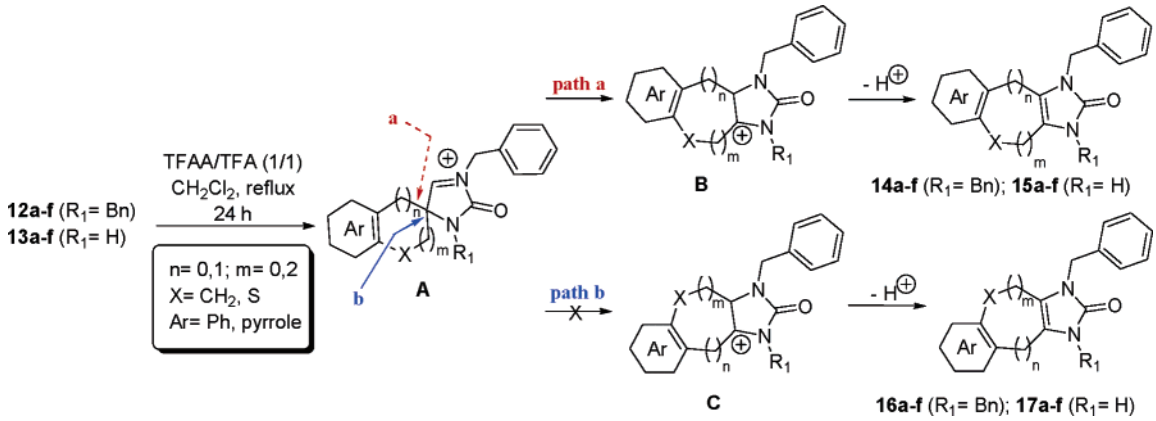
SCHEME 8. Mechanism of the Formation of Systems Containing an Imidazol-2-one Nucleus



11a−**g** was not effective because the reaction failed in some cases or gave a mixture of inseparable products containing the starting material. The same observations were made also when the reduction reaction was conducted at refluxing THF or diethyl ether in the case of spirohydantoins **10a**−**h** and when a cosolvent such as THF or diethyl ether was present in the cases of spirohydantoins **11a**−**g**.

The cyclization of the latter cyclic *N*-acyliminium precursors of general structures **12** and **13** with TFAA−TFA combination in precise proportion (1/1) provides a versatile short synthesis of two categories of 4,5-fused tricyclic and tetracyclic imidazolidin-2-ones **14** and **15** under mild conditions and via an interesting tandem transposition/π-cationic cyclization. The key step of this transformation is based on the formation of the cyclic *N*-acyliminium intermediates **A**, from which a transposition of the electronically rich group resulted in the ring expansion leading to a stable cyclic cation, which loses one proton spontaneously to give the title products **14** and **15**. Importantly, whatever the presence of serious competing reactions as shown in Schemes 1 and 8, the reaction seems to be clean and regiospecific. Furthermore, this tandem process seems to be general to cyclic *N*-acyliminium ions derived from spirobicyclic and spirotricyclic systems, compatible with a nonprotected nitrogen atom, and furnished the desirable products in good to excellent yields.

Finally, we anticipate that the novel transformations developed in this project, particularly the access to the substituted imidazolidin-2-ones of type **15**, will find further applications in synthesis using either the secondary amide chemistry directly or the sulfur chemistry via corresponding thioamides and their functionalization. Our products of type **15** are particularly adapted for these transformations as outlined in the Introduction. These systems are currently under investigation in our laboratory and will be reported soon.

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Supporting Information Available: Spectroscopic data of all compounds including ^{1}H NMR, ^{13}C NMR (DEPT program), and IR spectra and complete experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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