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Parham-type Cyclization and Nucleophilic Addition - *N*-Acyliminium ion Cyclization Sequences for the Construction of the Isoquinoline Nucleus

M. Isabel Collado, Nuria Sotomayor, María-Jesús Villa, and Esther Lete*

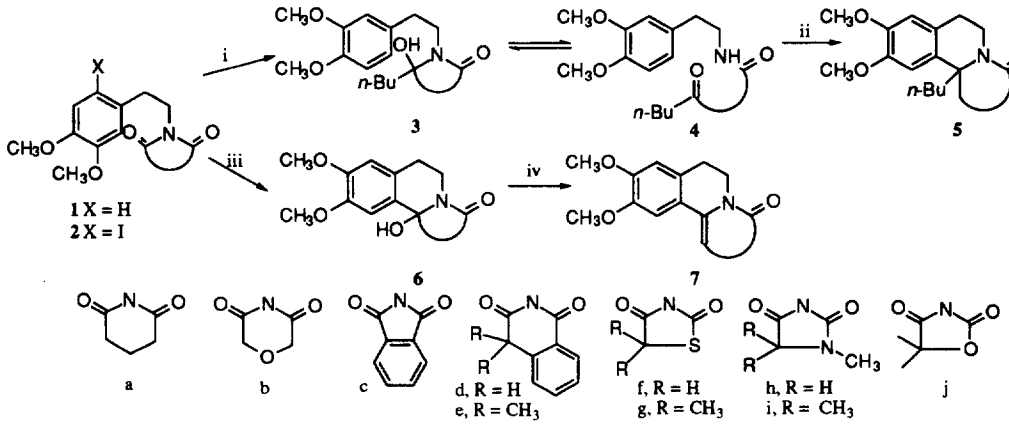
Departamento de Química Orgánica, Facultad de Ciencias, Universidad del País Vasco, Apdo. 644- 48080 Bilbao, Spain.

Abstract. Efficient methodologies based on the nucleophilic addition- *N*-acyliminium ion cyclization and the Parham-type cyclization sequences of *N*-phenethylimides **1** and **2** are reported for the synthesis of a variety of heterocyclic systems: benzo[a]quinolizidones and their 2-oxa analogs, isoindoloisoquinolones, dibenzo[a,h]quinolizidones, thiazolo-, oxazolo-, and imidazolo [4,3-a]isoquinolones.

Aromatic directed metalation reaction[1] and Parham-type cyclization[2] have proven to be effective methods for the construction of carbocyclic and heterocyclic systems. Advantage has been taken of the very fast rate of metal-halogen exchange compared with nucleophilic addition to certain carbonyl groups to synthesize 3-alkylidenephthalimidines[3] and 1-arylbenzo-cyclobutenols and cyclobutenes.[4] The recent demonstration[5] that organolithium reagents undergo addition to the carbonyl group of *N*-phenethylimides in preference to metal-hydrogen or metal-bromine exchange, while preferential metal-halogen exchange takes place on iodinated imides, allowed us to develop two basic strategies for the construction of the isoquinoline nucleus, the key steps being a nucleophilic addition-cyclization *via* *N*-acyliminium ions and Parham-type cyclization, respectively.

As a rational extension of this work into other synthetically useful fields, we have initiated the study of the reactivity of a series of *N*-phenethylimides **1** and **2**[6] towards organolithium reagents, and we report preliminary observations on lithiation-cyclization and nucleophilic addition-cyclization *via* *N*-acyliminium ions of these imides leading to several heterocyclic systems. These new processes constitute prototypes of regiospecific, mild, and potentially general approaches for the construction of isoquinoline alkaloids skeletons from imides using organolithium reagents, which supersede or effectively compete with the classical routes.

When imides **1a-c** were subjected to reaction with *n*-BuLi (2.1 equiv.), a smooth nucleophilic addition of the organolithium reagent was observed (entries 1-3, Table 1). A simple aqueous workup yielded the oxoamides **4a-b** (entries 1 and 2, Table 1) or their cyclic tautomer, hydroxylactam **3c** (entry 3) in excellent yields. Subsequent treatment of these addition products with TFA in dichloromethane at room temperature resulted in the quantitative formation of the corresponding isoquinoline derivatives: benzo[a]quinolizidone **5a**, its 2-oxa analog **5b**, and nuevamine-type isoindoloisoquinolone **5c** (entries 4-6, Table 1). Comparable yields of isoquinolines **5a-c** were obtained by quenching the *n*-BuLi addition reactions with TFA, though in some cases, conversions were lower. We reasoned that the cyclization took place *via* *N*-acyliminium ions, which could be easily formed by dehydration of the adducts **3** or **4** in acidic media.[7] The tertiary hydroxylactams are susceptible to dehydration and depending on the pH, enamides **8** could also be isolated.

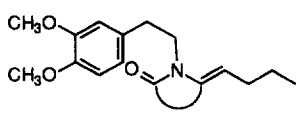


Scheme 1. Nucleophilic addition-*N*-acyliminium ion cyclization of imides **1** (X = H): (i) *n*-BuLi (2.1 equiv), THF, -78°C, 6h; then H_2O. (ii) TFA, CH_2Cl_2, rt or reflux, overnight. Lithiation-cyclization of imides **2** (X = I): (iii)*n*-BuLi (2.1 equiv.), THF, -78°C, 4h; then H_2O. (iv) TFA, CH_2Cl_2, rt or $CHCl_3$, reflux.

Table 1. Nucleophilic Addition-*N*-Acyliminium ion Cyclization of imides **1** (X = H) and Lithiation-Cyclization of imides **2**. (X = I)

Entry	Substrate	Method[a]	Product, yield (%)[b]
1	**1a**	A	**4a**, 99
2	**1b**	A	**4b**, 80
3	**1c**	A	**3c**, 92
4	**1a**	B	**5a**, 94
5	**1b**	B	**5b**, 93
6	**1c**	B	**5c**, 95
7	**2a**	C	**6a**, 83[c]
8	**2b**	C	**6b**, 88
9	**2c**	C	**6c**, 96

[a]Method A: *n*-BuLi (2.1 equiv.) added to **1a-c**, THF, 6h, -78°C, H_2O quench. Method B: *n*-BuLi added to **1a-c**, THF, 6h, -78°C; then TFA, CH_2Cl_2, rt, overnight . Method C: *n*-BuLi (2.1 equiv.) added to **2a-c**, THF, 4h, -78°C, H_2O quench. [b]Yields refer to isolated products of >95% purity. [c]Spontaneously dehydrated to **7a**.



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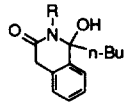
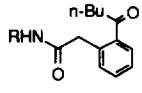
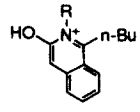
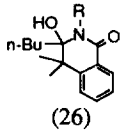
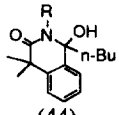
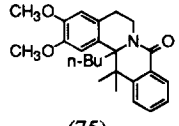
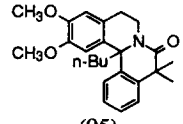
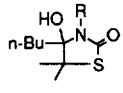
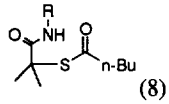
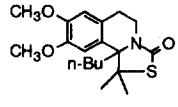
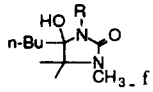
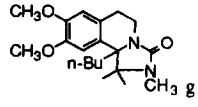
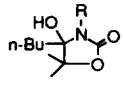
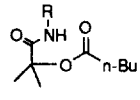
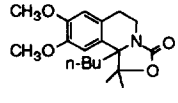
The application of Parham-type cyclization[2] to imides **2a-c** allowed the one-pot preparation of isoquinoline derivatives **6a-c**. It is of considerable interest that the benzo[a]quinolizidone **6a** spontaneously dehydrated to the cyclic enamide **7a**, while **6b** underwent rapid dehydration in acidic medium (TFA) to give **7b**.[8]

Both procedures have been shown to be extremely efficient for the intramolecular cyclization of these imides, affording interesting types of isoquinoline derivatives in good yields. Thus, benzo[a]quinolizidines, key intermediates in the synthesis of *Ipecac* alkaloids,[9] possess, in many cases, strong pharmacological activities.[10] It was in this context that we studied whether these protocols could be employed for the synthesis of more complex heterocyclic systems, as dibenzo[a,h]quinolizidones **5e** and **6e**, derived from homophthalimides **1e** and **2e**, respectively (Table 2).

The homophthalimide **1d** underwent rapid deprotonation at the benzylic position using the *n*-BuLi addition conditions (D_2O quench). Therefore, **1d** was converted in its silylenol derivative by deprotonation with *n*-BuLi (1.1 equiv) in THF at -78°C, followed by addition of TMSCl, and then treated with *n*-BuLi to provide a 1:1.5 mixture of hydroxylactam **3d** and oxoamide **4d**. However, when these *n*-BuLi addition products were submitted to cyclization with TFA, the 1-*n*-butyl-*N*-(3,4-dimethoxyphenethyl)-3-hydroxyisoquinolinium salt was obtained as the major product. In this case, the facile aromatization of the initially formed *N*-acyliminium salt prevented the cyclization. Under similar conditions, treatment with *n*-BuLi and TFA in sequence (Method B), the

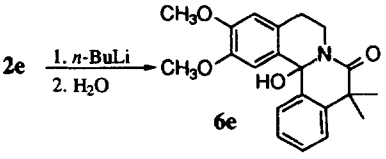
dimethylated homophthalimide **1e** afforded a 1:1.7 mixture of the corresponding protoberberinone and dibenzo[a,h]quinolizidinone **5e** (entry 2, Table 2). The organolithium addition to this unsymmetrical imide is attended with modest regioselectivity, with preferential addition to the less hindered carbonyl group. In all cases, the intermediate hydroxylactams and/or oxoamides could be isolated and fully characterized.[11]

Table 2. Nucleophilic Addition-*N*-Acyliminium ion Cyclization of imides **1** (R= 3,4-dimethoxyphenethyl)

Entry	Substrate	Nucleophilic Addition Products, [Yield (%)][a,b]		Cyclization Products, Yield (%)[a,b]
		Hydroxylactams 3	**Oxoamides 4**	**Lactams 5**
1	**1d**[c,d]	 (38)	 (58)	 (90)
2	**1e**[d]	 (26)  (44)	–	 (75)  (95)
3	**1g**[d,e]	 (75)	 (8)	 (95)
4	**1i**.	 [f]	–	 [g]
5	**1j**[d,e]	 (58)	 (16)	 (94)

[a]The reaction was carried out following Method B: *n*-BuLi (2.1 equiv.) added to **5d-j**, THF, 6h -78°C, H_2O quench; then TFA, $CHCl_3$, reflux , 1-4 days (entries 1-4) or TFA , CH_2Cl_2, rt, overnight (entry 5). [b]Yields refer to isolated products of >95% purity. [c]**1d** was first treated with *n*-BuLi (1.1. equiv) and TMSCl (1.1 equiv). [d]The isomers were separated by HPLC or flash column chromatography, identified, and cyclized. [e]Only the cyclic tautomer cyclized by treatment with TFA. [f]This compound was fully characterized from the crude because the reaction was quantitative; but on flash column chromatography it was dehydrated, affording the enamide **8i** in a 81% yield. [g]In this case, the yield could not be accurately calculated because **5i** (NMR detected) decomposed when submitted to column chromatography or HPLC.

Furthermore, the extension of both methodologies to other heteroatom-inserted imide derivatives was anticipated. It should be noted that heterocycle fused isoquinolines, such as thiazolo-, oxazolo-, and imidazolo-[4,3-a]isoquinolines, would be useful for the synthesis of functionalized isoquinolines and they also would be attractive for their potentially biological activities.[12] As shown in Table 2, addition of *n*-BuLi to heteroatom-inserted imides **1g**, **1i-j** occurred with high regioselectivity at the amide carbonyl group (entries 3-5, Table 2). Subsequent treatment of the cyclic adducts **3g**, **3i-j** with TFA provided quantitatively the corresponding heterocycle fused isoquinolines **5g**, **5i-j**, respectively, while the oxothioester **4g** and oxoester **4j** did not cyclize in acidic media



On the other hand, when the lithiation-cyclization sequence (Method C) was applied to the iodinated homophthalimide **2e**, the 13b-hydroxydibenzo[a,h]quinolizidin-6-one **6e** was isolated in a 66% yield, after recrystallization from ethyl ether. However, application of the lithiation-cyclization strategy to the iodinated heteroatom-inserted imides **2g**, **2i-j** resulted in intractable mixtures, probably due to the higher instability of cyclization products.

In summary, Parham-type cyclization and carbophilic addition - *N*-acyliminium ion cyclization sequences provide new routes for the synthesis of several types of isoquinoline alkaloids, starting from imides and organolithium reagents. Our methodologies offer convenient alternatives for the synthesis of benzo[a]quinolizidones and their 2-oxa analogs, isoindoloisoquinolones, dibenzo[a,h]quinolizidones, thiazolo-, oxazolo-, and imidazolo [4,3-a]isoquinolones, due to the high yields and mildness of experimental conditions. Besides, they would allow the introduction of a variety of substituents at the C-1 position of the isoquinoline nucleus, which is not readily achievable by others methods.

ACKNOWLEDGMENTS

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6. The requisite imide substrates **1a-d** were prepared by condensation of 3,4-dimethoxyphenethylamine with cyclic anhydrides, while imides **1f**, **1h**, and **1j** were prepared by the Mitsunobu reaction of 3,4-dimethoxyphenethyl alcohol and imides. Reaction of imides **1d**, **1f**, and **1h** with LDA/IMe yielded the **1e**, **1g**, and **1i**, respectively. Treatment of these *N*-phenethylimides with ICl in glacial acetic acid produced the iodinated derivatives **2** in high yields (75 - 95%).
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