

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

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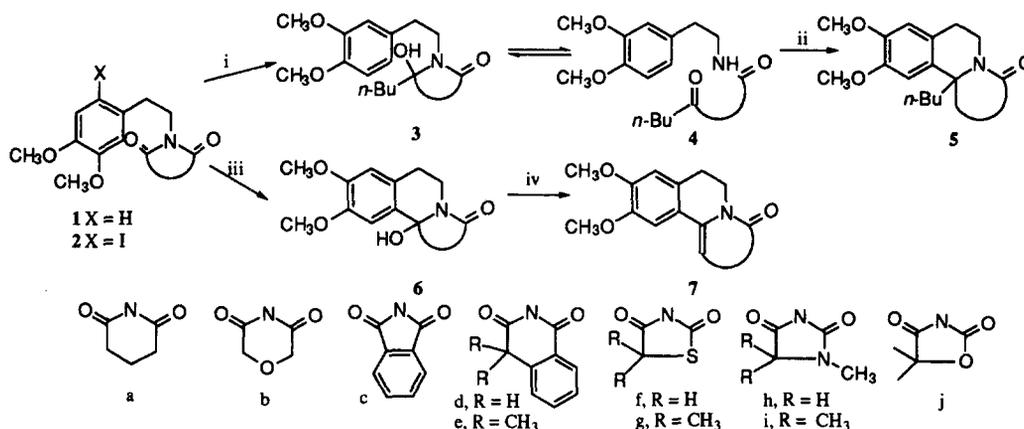
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Abstract. Efficient methodologies based on the nucleophilic addition- *N*-acylium ion cyclization and the Parham-type cyclization sequences of *N*-phenethylimides **1** and **2** are reported for the synthesis of a variety of heterocyclic systems: benzo[a]quinolizidones and their 2-oxa analogs, isoindoloisoquinolones, dibenzo[a,h]quinolizidones, thiazolo-, oxazolo-, and imidazolo [4,3-*a*]isoquinolones.
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Aromatic directed metalation reaction¹ and Parham-type cyclization² 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-alkylidene-phthalimides³ and 1-arylbenzo-cyclobutenols and cyclobutenes.⁴ The recent demonstration⁵ 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*-acylium 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*-acylium ions of these imides leading to several heterocyclic systems. These new processes constitute prototypes of regioselective, 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 neovamine-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*-acylium 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 H₂O. (ii) TFA, CH₂Cl₂, rt or reflux, overnight. Lithiation-cyclization of imides **2** (X = I): (iii) *n*-BuLi (2.1 equiv.), THF, -78°C, 4h; then H₂O. (iv) TFA, CH₂Cl₂, rt or CHCl₃, reflux.

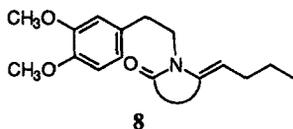
Table 1. Nucleophilic Addition-*N*-Acyliminium ion Cyclization of imides **1** (X = H) and Lithiation-Cyclization of imides **2**. (X = I)

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

^aMethod A: *n*-BuLi (2.1 equiv.) added to **1a-c**, THF, 6h, -78°C, H₂O quench. Method B: *n*-BuLi added to **1a-c**, THF, 6h, -78°C; then TFA, CH₂Cl₂, rt, overnight. Method C: *n*-BuLi (2.1 equiv.) added to **2a-c**, THF, 4h, -78°C, H₂O quench.

^bYields refer to isolated products of >95% purity.

^cSpontaneously dehydrated to **7a**.



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

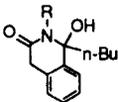
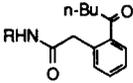
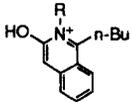
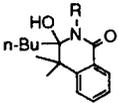
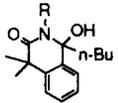
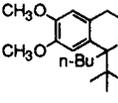
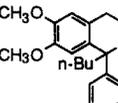
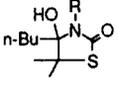
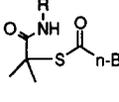
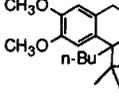
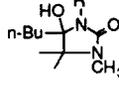
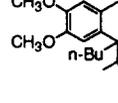
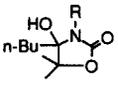
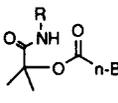
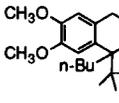
The application of Parham-type cyclization² to imides **2a-c** allowed the one-pot preparation of isoquinoline derivatives **6a-c**. It is of considerable interest that the benzo[*a*]quinolizidone **6a** spontaneously dehydrated to the cyclic enamide **7a**, while **6b** underwent rapid dehydration in 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 (D₂O quench).

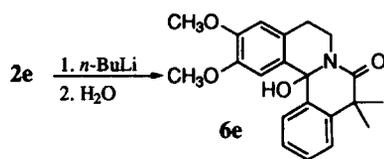
dimethylated homophthalimide **1e** afforded a 1:1.7 mixture of the corresponding protoberberinone and dibenzo[*a,h*]quinolizidinone **5e** (entry 2, Table 2). The organolithium addition to this unsymmetrical imide is attended with modest regioselectivity, with preferential addition to the less hindered 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	 (75)	-	 (95)		
5	1j,d,e	 (58)	 (16)	 (94)		

^aThe reaction was carried out following Method B: *n*-BuLi (2.1 equiv.) added to **5d-j**, THF, 6h -78°C, H₂O quench; then TFA, CHCl₃, reflux, 1-4 days (entries 1-4) or TFA, CH₂Cl₂, rt, overnight (entry 5). ^bYields refer to isolated products of >95% purity. ^c**1d** was first treated with *n*-BuLi (1.1 equiv) and TMSCl (1.1 equiv). ^dThe isomers were separated by HPLC or flash column chromatography, identified, and cyclized. ^eOnly the cyclic tautomer cyclized by treatment with TFA. ^fThis 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. ^gIn 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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