# Tandem Carbophilic Addition - *N*-Acyliminium ion Cyclization for the Synthesis of Functionalized Pyrrolo[2,1-a]isoquinolones: Key Intermediates for the Preparation of *Erythrina*-type Alkaloids

Izaskun Manteca, 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 . Sequential carbophilic addition of organolithium reagents- *N*-acyliminium ion cyclization of *N*-phenenethylsuccinimide **3** yields pyrrolo[2,1-a]isoquinolones **1** in high yields, with the possibility of varying the substituent at C-10b by changing the organolithium. Application of this methodology to the *cis*-norbor-5-en-2,3-dicarboximide **7** using a functionalized organolithium reagent, the 3-(2-trimethylsilyl-1,3-dithian-2-yl)propyllithium **11**, followed by desilylation and subsequent retro-Diels-Alder reaction affords the α,β-unsaturated pyrroloisoquinolone **9b**, immediate precursor of *Erythrina*-type alkaloids.
Copyright © 1996 Published by Elsevier Science Ltd

The intramolecular carbon-carbon bond forming reactions of *N*-acyliminium ions have found an impressive number of synthetic applications.[1] Such *N*-acyliminium ions have shown to be suitable intermediates in various types of intramolecular cyclization reactions using different types of π-nucleophiles.[2] Recently, we enhanced the scope of this chemistry by describing a method for preparing pyrroloisoquinolines **1** by a tandem carbophilic addition - *N*-acyliminium ion cyclization sequence from *N*-phenethyl succinimides and alkyllithiums.[3] The advantage of this strategy is that construction of the pyrroloisoquinoline nucleus may result in the introduction of functionality on the pendant side chain at C-10b, by the appropriate choice of the organolithium reagent at the first step. As an extension of this work, a series of *N*-phenethyl imides was employed in the synthesis of several isoquinoline alkaloids: 5-arylpyrrolo[2,1-a]isoquinolones, benzo[a]quinolizidines and their 2-oxa analogs, isoindoloisoquinolones, dibenzo[a,h]quinolizidones, thiazolo-, oxazolo-, and imidazolo [4,3-a]isoquinolones.[4]

Scheme 1
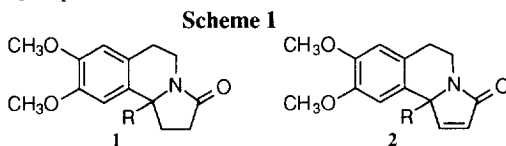
On the basis of these results, it was envisioned that this strategy could be applied to both higher functionalized imides and organolithium compounds, which would make possible the access to unsaturated lactams **2**, immediate precursors of *Erythrina* type alkaloids[5] by intramolecular conjugated addition.[6] We wished to develop a one-step approach to these lactams **1** and **2** with the ability to vary the substituents at C-10b. With this goal in mind, we embarked upon the application of a tandem carbophilic addition - *N*-acyliminium cyclization sequence for the synthesis of substituted pyrroloisoquinolones. We now wish to present our initial findings from our investigations of this tandem sequence.

The model succinimide **3**[3] was treated with a range of organolithium reagents in order to study the influence of steric and electronic effects in both the addition and cyclization steps. Addition reactions were

carried out with 2.2 equivalents of the organolithium reagent at -78°C over 6 h, and quenched with water. After work-up, equilibrium mixtures of the hydroxy lactams **4** and the corresponding tautomeric oxo amides **5** were obtained, as summarized in Table 1 (Scheme 2). The fact that no open-chain hydroxyamides resulting from RLi attack to the ketone carbonyl in **5** have been detected, suggests that these oxo amides **5** are formed during aqueous work-up, and not by ring opening of the intermediate lithium alkoxide. In cases **a** and **b** (entries 1 and 2, Table 1), the tautomers **4** and **5** could be chromatographically separated and identified by NMR. However, since the subsequent cyclization of both compounds can lead to the same pyrroloisoquinolone, no previous separation is required and NMR resonances can be used in the determination of the tautomers ratio from the mixture. The most significant signal were the NH triplet for the oxo amides **5** (5.70 ppm for **5a**) in the ^{1}H NMR spectrum and the ^{13}C NMR chemical shift of the carbinolic or ketonic carbon (i.e. 89.72 ppm for **4a** and 209.80 for **5a**, respectively).
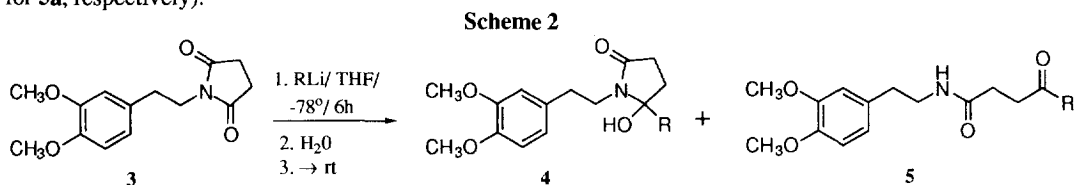
Scheme 2

Table 1. Products from the RLi Carbophilic Addition Step of the Sequence with **3**

Entry	RLi[a]	Products		
		R	Yield (%)[b]	Ratio **4** / **5**[c]
1	MeLi	**a**, Me	87	4.8 / 1
2	n-BuLi	**b**, n-Bu	61	4.2 / 1
3	s- BuLi	**c**, s-Bu	52	d
4	Me$_3$SiCH$_2$Li	**a**, Me	60	4.8 / 1
5	PhLi	**d**, Ph	95	1 / 3
6	PhC≡CLi	**e**, PhC≡C	61	e
7	CH$_2$=CHCH$_2$Li	**f**, CH$_2$=CHCH$_2$	f	1.9 / 1
8	CH$_2$=CHLi	**g**, CH$_2$=CH	f	1 / 1.4

[a] All RLi are commercially available, except allyl and vinyl lithium, prepared by transmetalation of the corresponding stannane.[7]

[b] Isolated yields of the mixture of tautomers **4** and **5**.

[c] Determined by ^{1}H NMR spectroscopy.

[d] Ratio could not be determined due to overlapping of signals in the ^{1}H NMR spectrum.

[e] Only the oxo amide **5** was isolated.

[f] Yields could not be accurately calculated due to contamination with the stannane derivative formed in the transmetalation, but conversion was complete and NMR spectra only showed signals due to the tautomers and the organotin compound.

Both yield and product distribution are affected by the steric and, above all, electronic nature of the carbon atom directly attached to the metal in the alkyllithium used as nucleophile. The ratio of oxo amides **5** slightly increases with the substitution (entries 1 and 2), whereas the hybridization change exerts a profound effect, inverting the ratio **4** / **5**. In fact, the hydroxy lactams **4d**, **4e**, and **4g** (entries 5, 6 and 8) are more unstable due to inductive effects on C-4, which favor the equilibrium towards the open chain isomer **5**.[8] The use of Me$_3$SiCH$_2$Li (entry 4) afforded a mixture of **4a** and **5a** (R= Me) in identical ratio to the one obtained with MeLi (entry 1). This result can be rationalized assuming that a carbon to oxygen migration of the trimethylsilyl group[9] had occurred, followed by hydrolysis of the O-Si bond during work-up.

Cyclization of the tautomeric mixture of **4** and **5** was accomplished with TFA in CH$_2$Cl$_2$ to afford the desired C-10b-substituted tetrahydropyrroloisoquinolones **6** (Scheme 3). As shown on Table 2, high cyclization

yields were obtained (except entries 5 and 7), though the rate was strongly influenced by the nature of the substituent R. Higher temperatures and longer reaction times are required when the steric bulk increases (entry 1 *vs.* 2 and 3) or when the R group makes less electrophilic the intermediate *N*-acyliminium ion by resonance effect (entries 6, 7, and 8).
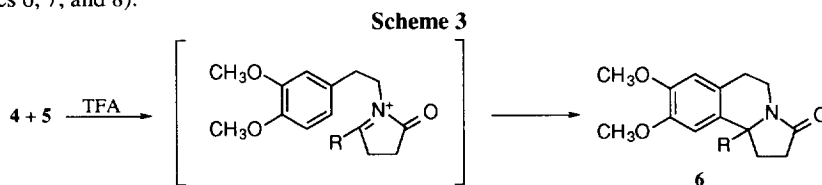
Scheme 3

**Table 2.** Products from the Cyclization step of **4 + 5**

Entry	Substrate	Conditions [time (h), T]	Prod.	Yield[a] (%)
1	**4a + 5a**	4, rt	**6a**	98
2	**4b + 5b**	18, reflux	**6b**	95
3	**4c + 5c**	72, reflux	**6c**	93
4	**4d + 5d**	36, reflux	**6d**	98
5	**5e**	72, reflux	**6e**	34[b]
6	**4f + 5f**	6, reflux	**6f**	97
7	**4g + 5g**	c	**6g**	c

[a] Yields refer to isolated products of >95% purity based on GC-MS analysis.

[b] Starting material was recovered.

[c] A mixture of products was obtained under various reaction conditions,

Once the reaction conditions had been set, access to the corresponding unsaturated pyrroloisoquinolines **2** was required. Direct lithiation of *N*-[(3,4-dimethoxyphenyl)]ethyl]maleimide[10] led only to polymerization products. In fact, these reaction conditions do not differ from the ones used in anionic polymerization of related substrates.[11] However, the *cis*-norbor-5-en-2,3-dicarboximide[10] **7** (Scheme 4) proved to be a suitable substrate, bearing a masked α, β-unsaturated imide moiety. Thus, the unsaturated pyrroloisoquinoline **9a** was successfully obtained upon treatment of **7** with *n*-BuLi, followed by TFA cyclization and retro-Diels-Alder reaction (Scheme 4). Subsequently, the organolithium **11** was chosen as nucleophile, as it carries an adequate

functionality[12] and would give rise to C-10b-substituted pyrroloisoquinolines that could be immediate precursors of the *Erythrina* skeleton.
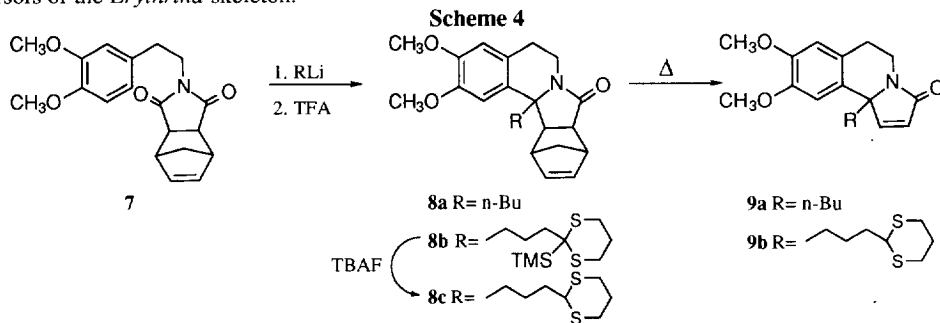
Scheme 4

Scheme 5

The organolithium reagent **11** was obtained by reductive lithiation[13] of **10**, readily prepared from commercially available products (Scheme 5), and *in situ* reacted with the imide **7** to afford **8b**, after treatment

with TFA (31% overall yield, conversion 80%). In this case, removal of the TMS protecting group with TBAF, prior to retro Diels-Alder reaction afforded **9b** quantitatively.

In summary, we have shown the viability of a tandem carbophilic addition - N-acyliminium cyclization sequence for the assembly of pyrroloisoquinolones, with the ability to vary the substituent at C-10b, by the appropriate choice of the organolithium reagent. The application of this methodology to the *cis*-norbor-5-en-2,3-dicarboximide **7** have allowed us to prepare dihydropyrroloisoquinolone **9b**, immediate precursor of *Erythrina*-type alkaloids.

ACKNOWLEDGMENTS

REFERENCES AND NOTES

1. Reviews: (a) Speckamp, W. N. *Rec. Trav. Chim. Pays-Bas* **1981**, *100*, 345-354. (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367-4416. (c) Hiemstra, H.; Speckamp, W. N. In *The Alkaloids*; Academic Press: New York, 1988; vol. 32, pp. 271-339. (d) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I. Eds.; Pergamon Press: Oxford, 1991; vol. 2; pp. 1047-1082. (e) Maryanoff, B. E.; Rebarchak, M. C. *Synthesis* **1992**, 1245-1248 and references therein.

2. For representative examples of π-nucleophiles, see: ref 1. For some recent examples, see: (a) Heaney, H.; Shuhaibar, K. F. *Synlett* **1995**, 47-48. (b) Lee, Y. S.; Kang, D. W.; Lee, S. J.; Park, H. *J. Org. Chem.* **1995**, *60*, 7149-7152. (c) Li, W. H.; Hanau, C. E.; Davignon, A.; Moeller, K. D. *J. Org. Chem.* **1995**, *60*, 8155-8170. (d) Logers, M.; Overman, L. E.; Welmalker, G. S. *J. Am. Chem. Soc.* **1995**, *117*, 9139-9150. (e) Marson, C. M.; Pink, J. H.; Smith, C. *Tetrahedron Lett.* **1995**, *36*, 8107-8110. (f) Rigo, B.; Elghammarti, S.; Couturier, D. *Tetrahedron Lett.* **1996**, *37*, 485-486. (g) Yamada, H.; Aoyagi, S.; Kibayashi, C. *J. Am. Chem. Soc.* **1996**, *118*, 1054-1059.

3. Lete, E.; Egiarte, A.; Sotomayor, N.; Vicente, T.; Villa, M. J. *Synlett*, **1993**, 41-43.

4. (a) Collado, M. I.; Lete, E.; Sotomayor, N.;Villa, M. J. *Tetrahedron* **1995**, *51*, 4701-4710. (b) Collado, M. I.; Sotomayor, N.; Villa, M. J.; Lete, E. *Tetrahedron Lett.* **1996**, in press.

5. Bentley, K. W. *Nat. Prod. Rep.* **1994**, *11*, 555-576 and refences cited therein.

6. (a) Hanessian, S.; Gomtsyan, A.; Payne, A. Hervé, Y.; Beaudoin, S. *J. Org. Chem.* **1993**, *58*, 5032-5034. (b) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814-3819.

7. Seyferth, D.; Weiner, M. A. *J. Org. Chem.* **1961**, *26*, 4797-4800.

8. Maryanoff, D. F.; McComsey, D. F.; Dhul-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062-5074.

9. (a) Brook, A. G. *Acc. Chem. Res.* **1974**, *7*, 77-84. (b) Hudrlick, P. F.; Peterson, D.; Rona, R. J. *J. Org. Chem.* **1975**, *40*, 2263-2264. (c) Tietze, L. F.; Geisler, H.; Gewert, J. A.; Jacobi, U. *Synlett* **1994**, 511-512.

10. N-[(3,4-dimethoxyphenyl)]ethylmaleimide and N-[(3,4-dimethoxyphenyl)]ethyl-*cis*-norbor-5-en-2,3-dicarboximide (**7**) were prepared by condensation of the N-(3,4-dimethoxyphenyl)ethylamine with the corresponding anhydride in refluxing acetic acid.

11. Heilmann, S. M.; Rasmussen, J. K. W. N. In *Comprehensive Heterocyclic Chemistry*, Katritzsky, A. R.; Rees, C. W.; Meth-Cohn, O. Eds.; Pergamon Press: Oxford, 1984; vol. 1; pp. 269-346.

12. α-Lithium dithianes have been reported to give 1,4 conjugated additions: (a) Schultz, A. G. Yee, Y. K. *J. Org. Chem.* **1976**, *41*, 4044-4045. (b) Prodger, J. C.; Bulmann Page, P. C.; van Niel M. B. *Tetrahedron* **1989**, *45*, 7643-7677. (c) Forns, P.; Díez, A.; Rubiralta, M.; Solans, X.; Font-Bardia, M. *Tetrahedron*, **1996**, *52*, 3563-3574.

13. Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 52-161, and references therein.