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Tandem Parham cyclisation—α-amidoalkylation reaction in the synthesis of the isoindolo[1,2-*a*]isoquinoline skeleton of nuevamine-type alkaloids

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Abstract—C-12b substituted isoindolo[1,2-*a*]isoquinolones **4** are prepared efficiently via a tandem Parham cyclisation—α-amidoalkylation reaction. Thus, Parham cyclisation on imide **1** generates a 12b-hydroxy isoindolo[1,2-*a*]isoquinolone, which is an immediate precursor of an *N*-acyliminium ion. Intermolecular alkylation with different π-nucleophiles (allyl silanes or enol ethers) is accomplished upon treatment with Lewis acids ($BF_3{\cdot}OEt_2$, $TiCl_4$) to obtain nuevamine-type derivatives in high yields (69–95%) under mild conditions.

The aromatic metallation–cyclisation sequence is a valuable protocol for the regiospecific construction of carbocyclic and heterocyclic systems. In addition to carbon–carbon bond formation, aromatic lithiation allows the introduction of further functionality to the molecule. Therefore, strategies based upon aromatic lithiation can play a crucial role in natural product synthesis. Aromatic lithiation can be carried out by lithium–hydrogen or lithium–halogen exchange.[1] The latter procedure, though mechanistically controversial,[2] is the method of choice to introduce regiospecifically a lithium atom into a given, nonactivated position of the aromatic ring. Once generated, the aryllithiums may react with external or internal electrophiles and thus give rise to cyclisation reactions, which are known as Parham cyclisations.[3] In this context, we had previously shown that iodine–lithium exchange could be performed on iodinated *N*-phenethylimides, allowing the construction of the isoquinoline nucleus via a Parham-type cyclisation. Since the fused isoquinolones so-obtained possess an α-hydroxylactam function, they would represent immediate precursors of bicyclic *N*-acyliminium ions,[4] which could be transformed into a variety of derivatives via an intermolecular α-amidoalkylation reaction. We wish to report here on the construction of isoindolo[1,2-*a*]isoquinolones **4**, using a tandem Parham cyclisation—α-amidoalkylation reaction.[5] C-12b substituted isoindolo[1,2-*a*]isoquinolones are interesting due to the actual and potential biological activities of many of their derivatives, such as isoindolobenzazepine alkaloids,[6] and dibenzo[*c*,*f*]azonines.[7] Thus, for instance, the latter derivatives are useful as central nervous system stimulants and antiinflammatories. In related strategies, isoindoloisoquinolones have been accessed by *N*-acyliminium ion cyclisation[8] or by intramolecular Heck reaction.[9] Other procedures, such as intramolecular condensation of a carboxylic acid and an amine,[10] Friedel–Crafts acylation[11] or palladium catalysed cabonylation processes[12] have been used occasionally.

The known imide **1**[13] was first converted into the isoindolo[1,2-*a*]isoquinolone **2** by Parham cyclisation using 2.2 equiv of *n*-BuLi at −78 °C (Scheme 1). Initial experiments to test the suitability of **2** as a precursor of the *N*-acyliminium ion **3** were carried out using the $NaBH_4$–TFA, reagent that has proven to be synthetically valuable for the reduction of hydroxy groups.[14] Thus, reduction of **2** was achieved by treatment with $NaBH_4$–TFA at 0 °C to afford the corresponding isoindolo[1,2-*a*]isoquinolone **4a**[15] in almost quantitative yield. It

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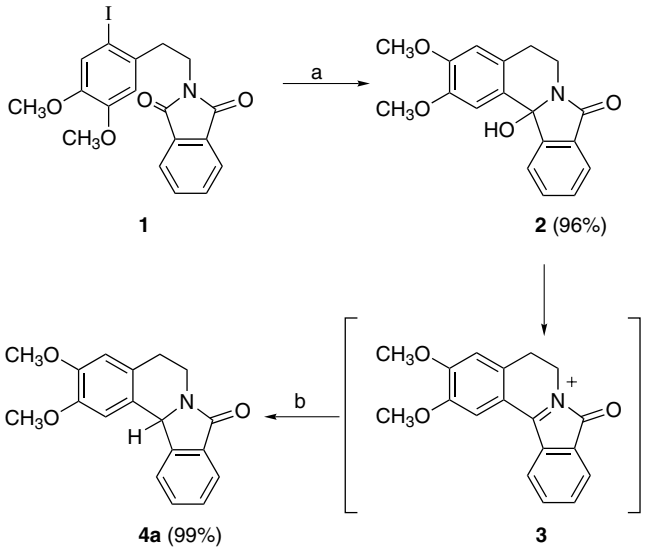


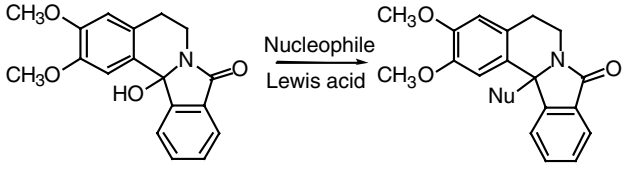
Scheme 1. Reagents and conditions: (a) *n*-BuLi, THF, −78 °C, 4 h; $NaBH_4$, TFA, 0 °C to rt, 1 h.

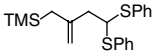
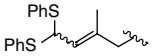
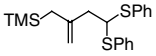
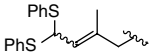
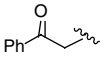
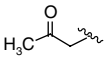
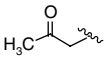
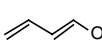
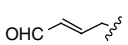
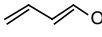
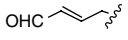
should be mentioned that the reaction could be easily monitored, since the *N*-acyliminium intermediate possesses a deep purple colour.

Next, the bicyclic α-hydroxylactam **2** was submitted to intermolecular α-amidoalkylation conditions using different types of π-nucleophiles, such as allylsilanes or silyl enol ethers, in the presence of Lewis acids. Table 1 summarises the results of our experiments. The reaction was first tested with allyltrimethylsilane using various Lewis acids to generate the *N*-acyliminium ion (TMSOTf, $TiCl_4$, $BF_3{\cdot}Et_2O$). Thus, to a solution of **2** and allyltrimethylsilane in dichloromethane at −78 °C, the Lewis acid (4 equiv) was added and after 12 h the reaction mixture was allowed to warm to room temperature (method A). As shown in the table, after some experimentation, we found that $TiCl_4$ was the best Lewis acid for the reaction with allylsilane. No reaction was observed with $BF_3{\cdot}OEt_2$, and very low conversion (20%) occurred with TMSOTf.[16]

In view of these results, we felt that extension of the method to more complex allylsilanes might provide access to novel analogues with potentially interesting properties. Thus, we chose 4,4-bisphenylsulfanyl-2-trimethylsilylbut-1-ene (entry 2), which had been previously prepared in our group,[17] via alkylation of bis(phenylthio)methane with 4-chloro-2-(trimethylsilylmethyl)-prop-1-ene. However, direct adoption of the conditions used for the conversion of **2** to **4b** did not lead to the desired α-amidoalkylation product and starting material was recovered. After extensive screening of conditions, it was found that generation of the *N*-acyliminium ion prior to the addition of the functionalised allylsilane was required. Thus, $TiCl_4$ (2 equiv) was added to a solution of **2** in dichloromethane at −78 °C and after 1 h, the nucleophile was added, then,

Table 1. Intermolecular α-amidoalkylation reaction of α-hydroxylactam **2**



Entry	Nucleophile	Lewis acid	Method[a]	Product	Nucleophile	Yield (%)
1		$TiCl_4$	A	**4b**		95
2		$TiCl_4$	A	**4c**		[b]
3		$TiCl_4$	B	**4c**		69
4		$TiCl_4$	A	**4d**		82
5		$TiCl_4$	A	**4e**		[b]
6		$BF_3{\cdot}OEt_2$	B	**4e**		81
7		$BF_3{\cdot}OEt_2$	A	**4f**		[b]
8		$BF_3{\cdot}OEt_2$	B	**4f**		81

[a] Method A: Lewis acid was added to a solution of **2** and nucleophile in CH_2Cl_2 at −78 °C. Method B: Lewis acid was added to a solution of **2** in CH_2Cl_2 at −78 °C. After 1 h, the nucleophile was added.
[b] Starting material was recovered.

the reaction mixture was allowed to warm to room temperature (method B), thus providing **4c** as a 1:1 mixture of *cis*/*trans* diastereomers in good yield.

At this stage we decided to test the behaviour of silyl enol ethers as nucleophiles in this α-amidoalkylation reaction. We found that reaction of **2** with 1-phenyl-1-silyloxyethene could be carried out using $TiCl_4$ under the conditions described for allyltrimethylsilane (method A).[18] However, when the reaction was carried out with 2-trimethylsilyloxypropene, starting material was recovered under these conditions (entry 5), and the enol ether was observed to polymerise. The best results were obtained when the *N*-acyliminium ion was previously formed with $BF_3{\cdot}OEt_2$ using method B. Similar results were obtained with 1-trimethylsilyloxy-1,3-butadiene (entries 7 and 8), with polymerisation of the enol ether occurring with method A using $BF_3{\cdot}OEt_2$, $TiCl_4$, TMSOTf or $SnCl_4$.

In summary, the tandem Parham cyclisation—α-amidoalkylation reaction constitutes an effective route to several nuevamine-type alkaloids, starting form the same imide, with the ability to introduce a variety of R substituents at the new quaternary position of the isoindolo[1,2-*a*]isoquinoline unit by changing the nucleophile used in the α-amidoalkylation step. Compared to other methods described in the literature,[8–12] our procedure is more flexible. In fact, some do not allow the introduction of substituents at C-12b, while others require changing the substrate, which usually implies complex and lengthy synthetic sequences. Only in the case of using the organometallic reagent addition—*N*-acyliminium ion cyclisation sequence,[13,19] it is easily possible to change the substituent at C-12b. However, the latter method would involve the preparation of functionalised organolithium reagents to access the desired heterocycles. Therefore, our method reduces the number of steps and simplifies the synthesis of this type of alkaloid.

Acknowledgements

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18. Typical procedure: Synthesis of 2,3-dimethoxy-12b-(2-oxopropyl)-5,12b-dihydro-6*H*-isoindolo[1,2-*a*]isoquinolin-8-one (**4d**): 1-phenyl-1-(trimethylsilyloxy)ethene (0.35 mL, 1.7 mmol) and $TiCl_4$ (0.09 mL, 0.87 mmol) were added sequentially to a solution of **2** (133 mg, 0.43 mmol) in dry CH_2Cl_2 at −78 °C. The reaction mixture was stirred at this temperature for 2 h, and allowed to reach rt. After 24 h, the reaction was quenched by the addition of saturated $NaHCO_3$ (15 mL). Standard work-up followed by flash column chromatography (silica gel, 40% hexane/ethyl acetate) afforded isoindoloisoquinoline **4d** (146 mg, 82%): IR (KBr): 1680 cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) (δ, ppm): 2.70–2.78 (m, 1H), 2.96–3.09 (m, 1H), 3.37 (td, $J = 12.5$, 4.6 Hz, 1H), 3.79–3.88 (m, 2H), 3.84 (s, 3H), 3.93 (s, 3H), 4.53 (dd, $J = 13.4$, 6.4 Hz, 1H), 6.59 (s, 1H), 7.23 (s, 1H), 7.31–7.38 (m, 2H), 7.40–7.52 (m, 2H), 7.57 (t, $J = 7.5$ Hz, 1H), 7.66 (d, $J = 7.9$ Hz, 2H), 7.79 (d, $J = 7.5$ Hz, 1H), 7.87 (d, $J = 7.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.8 MHz) (δ, ppm): 28.7, 35.4, 47.1, 55.7, 56.1, 64.7, 109.3, 111.8, 122.6, 123.6, 126.0, 127.7, 128.3, 129.2, 131.5, 131.7, 133.0, 137.2, 147.5, 148.0, 148.3, 167.9, 195.7. MS (EI) m/z (%): 413 (M^+, 3), 295 (25), 294 (100), 279 (4), 278 (8), 250 (8), 151 (3), 77 (4). HRMS calcd for $C_{26}H_{23}NO_4$: 413.1627; found: 413.1615.
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