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Synthesis of benzo(or furo)[5,6]azepino[2,1-a]isoindolone derivatives: π-cyclisations of *N*-acyliminium ions.

Adam Daïch*[a], Stefan Marchalin[b], Pascal Pigeon[a], Bernard Decroix[a]

a) Laboratoire de Chimie, Faculté des Sciences et Techniques de l'Université du Havre, 25 rue Philippe Lebon, 76058 Le Havre Cedex, France.

b) Department of Organic Chemistry, Slovak Technical University, Radlinského 9, 81237 Bratislava, Slovakia.

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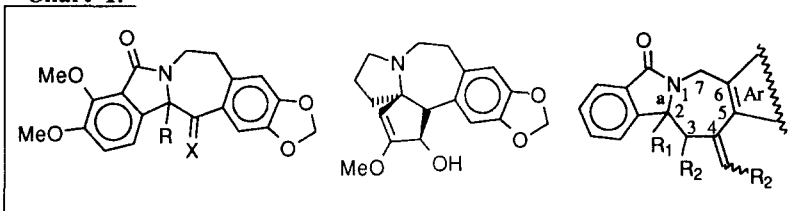
Abstract:

Benzo(or furo)[5,6]azepino[2,1-a]isoindolone and derivatives were obtained easily in one-pot *via* N-acyliminium ions by treatment of 2-(2-methoxycarbonylbenzyl(or fur-3-yl))phthalimide with alkylmagnesium iodide followed by an acidic hydrolysis.

Keywords: Grignard reagents-Olefins-Azepines-Furans.

Because of their potential biological properties, benzazepines and derivatives annelated to an isoindole or pyrrolidine ring as in numerous natural alkaloids, have attracted considerable interest in recent years. These structures were exemplified by Chilenine **1** [1,2,3], Lennoxamine **2** [1,4] extracted from Chilean Berberidaceae, *Berberis darwinii* Hook and Cephalotaxine **3** [5] isolated from *Taxus baccata* (Chart 1).

Chart 1.



1 R=OH, X=O Chilenine
2 R=H, X=H2 Lennoxamine

3 Cephalotaxine

4 R_1=Me, R_2=H
5 R_1=Et, R_2=Me

Our previous studies on the synthetic utility of amidoalkylation reactions [6,7] *via* π-cyclisations of *N*-acyliminium ions together with our interest in the development of synthetic approaches to diversely substituted polyheterocyclic systems, allowed us to report the first preparation of benzo(or furo)azepinoisoindolone **4** or **5** (Chart 1). These latter bear an

* fax: (+33) 02-35-19-67-71, phone: (+33) 02-35-19-67-54.

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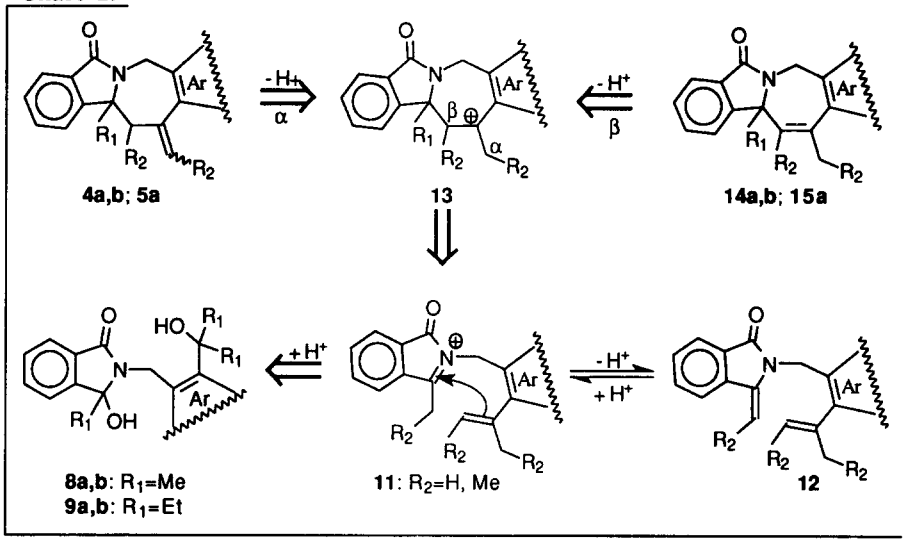
exocyclic double bond and an angular alkyl group and were prepared in one-pot reaction using an imide-ester functionality as precursor.

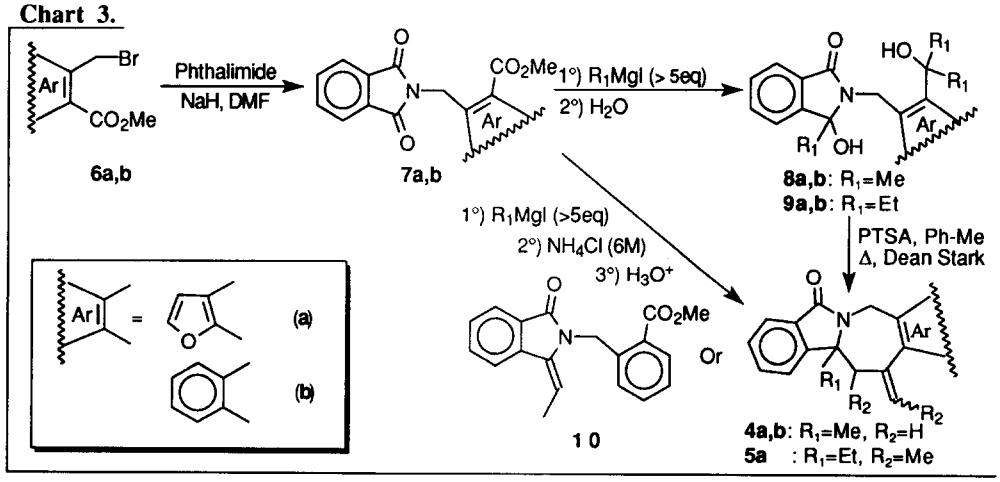
If benzo(or thieno)azepinoisoindolones [8] with an exocyclic olefin are few reported in literature in contrast to those with an endocyclic one [1,2,8-10], in our knowledge no report have been done on the chemistry of furoazepines fused to an isoindole ring.

Chart 2.



Indeed, taking into account that hydroxylactams and tertiary alcohols functions (**8a,b** and **9a,b**) generate respectively N-acyliminium ions and olefins (**11**) in acidic medium [11,12]. The ring closure could take place through an intramolecular α-amidoalkylation cyclisation with olefin as internal nucleophile in intermediate **11** leading to the stabilised benzylic type carbocation **13** (Chart 2). The latter could also be obtained from **12** in equilibrium with **11** in acidic conditions. Finally, the loss of the proton attached to C_α carbon gave the title compounds **4** or **5** rather than the regioisomers **14** or **15** with an endocyclic double bond.

Chart 3.

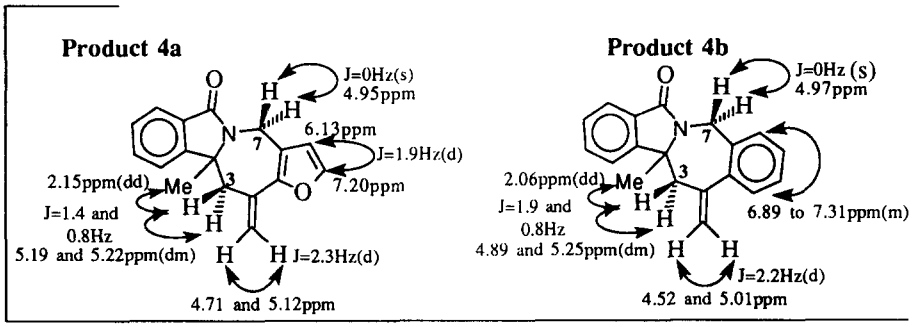


As depicted in chart 3, imide-esters **7a** and **7b** [13] (obtained by classical condensation of phthalimide with the known methyl 3-bromomethylfurane-2-carboxylate **6a** [14] and methyl o-bromomethylbenzoate **6b** [15]) were reacted with more than 5 equivalents of freshly prepared methylmagnesium iodide at 0-5°C for 3 hours. This yielded after water hydrolysis the hydroxylactam-alcohols **8a** and **8b** in good yields (71 and 78% respectively). Moreover, an acidic hydrolysis gave directly the cyclised products as **4a** and **4b** in 79 and 83% yields. The rate of the Grignard reaction decreased at lower temperature (< 0°C) whatever the nature of solvent used (tetrahydrofuran, diethyl ether or dichloromethane) but when the temperature rised to room temperature, dehydration reactions of hydroxylactam and alcohol functions took place giving a complexe mixture of unseparable products. Nevertheless, heating pure **8a** or **8b** under azeotropic conditions in dry toluene with a catalytic amount of PTSA furnished after flash chromatography purification on silica gel the same tetracyclic azepine **4a** or **4b** (55 and 70% respectively) (Chart 3).

Under similar conditions as above, with ethylmagnesium iodide as the Grignard reagent, the imide-ester **7a** led to ω-ethyl-ω-carbinol lactam **9a** (73% yield) which cyclised under azeotropic conditions into tetracyclic azepine **5a** (62% yield). The same product was obtained from **7a** under one-pot cyclisation conditions (78% yield). From **7b**, the formation of diol **9b** was never observed whatever the quantity of ethylmagnesium iodide (> 5 equivalents) but under the one-pot cyclisation conditions, **7b** led only to the dehydration product **10** in 82% yield.

The typical reaction leading in one-pot to the title products (78 to 83% yield), was performed by addition of more than 5 equivalents of alkylmagnesium iodide to imide-ester **7** under stirring in dry dichloromethane followed by hydrolysis for 30 minutes with 6M ammonium chloride solution and then with a diluted hydrochloric or sulfuric acid solution for an additional 1 hour. After a classical work up, the structures of the isolated intermediates **8-10** and final products **4a,b** and **5a** were well established by their ir, ^{1}H and ^{13}C nmr spectra (200 MHz), mass spectra as well as by their microanalyses (Chart 4).

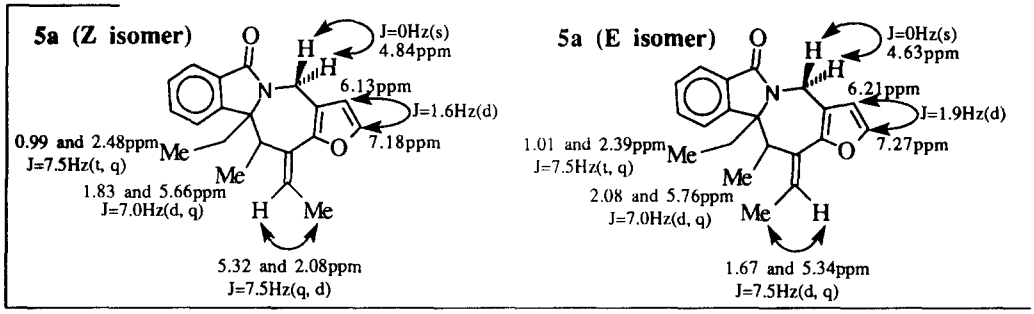
Chart 4.



The methylidene hydrogens in **4a** appear as a doublet with the characteristic coupling constant of J=2.3 Hz, the C_7 protons appear as a singlet while the C_3 protons appear as two multiplets (the protons are non equivalents and are coupled with the angular methyl group as indicated by both decoupling and 2D symmetric COSY experiments) with coupling constants

of J=1.4 and J=0.8 Hz. Likewise, the ^{13}C nmr spectra of **4a** reveals the presence of the exomethylene carbon in aromatic region at δ=113.7 ppm which inverts in the corresponding DEPT program spectrum (similar observations can be made in the ^{1}H and ^{13}C nmr spectra of compound **4b**). For **5a**, the ^{1}H nmr spectrum shows a non separable 78/22 mixture of Z and E isomers. The assignments of Z or E configuration is based on the nmr data of related compounds [15-18](Chart 5).

Chart 5.



In summary, a straightforward and efficient synthesis of functionalised furoazepino-isoindolones **4a,5a** and benzoazepinoisoindolone **4b** bearing an angular alkyl group were described from imide-esters **7a,b** in one-pot reactions with alkylmagnesium iodide. Further studies of the addition of various organometallic reagents are in progress and the results will be published soon.

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