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NEW FEATURES OF THE INTRAMOLECULAR DIELS ALDER ROUTE TO HYDROISOINDOLES

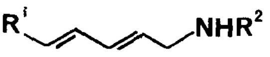
John M Mellor* and Alison M Wagland
Department of Chemistry, The University, Southampton, SO9 5NH.

Abstract: Regio- and stereo- controlled routes to functionalised hydroisoindoles have been developed by reaction of aminodienes with unsaturated anhydrides or acid chlorides and subsequent elaboration of the Diels Alder adducts.

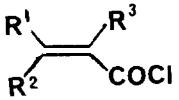
A recent publication[1] notes the limited use of the intramolecular Diels Alder (IMDA) reaction in the construction of nitrogen heterocycles, and in particular, hydroisoindoles, and describes improved stereoselective routes to such targets. Such limitations contrast with the more advanced use of the IMDA reaction in the construction of carbocycles[2], or lactones[3,4] from esters. The French authors note the limitations of both the lack of stereocontrol in earlier IMDA reactions, and the relative difficulty in synthesis of the required triene precursors for construction of hydroisoindoles. To these limitations may be added the lack of development of routes leading to functionalised hydroisoindoles. Whereas in the construction of bicyclic lactones strategies have been developed based on the incorporation of extra functionality into both the diene[4] and the dienophile[3] units, with limited exceptions[5], such studies have not been made relating to the synthesis of hydroisoindoles. In this paper we describe the use of a number of dienophilic partners in the IMDA reaction. By reaction with suitable aminodienes we can now report the synthesis of a wide variety of functionalised bicyclic adducts, and by subsequent elaboration of the appropriate adducts effective regio- and stereocontrolled routes to unusual hydroisoindoles.

The results[6] are shown of the reaction of the aminodienes (1-5) with dichloromaleic anhydride (6) in Table 1, and with the other potential dienophiles acryloyl chloride (7) in Table 2 and maleic anhydride (8), bromomaleic anhydride (9) and the esters (10-13) in Table 3. In all cases, in agreement with earlier studies, reactions are considered to proceed via initial amide formation followed by IMDA reaction. In certain cases the intermediate acyclic amides were isolated but the adducts are generally conveniently prepared without isolation of such intermediates.

Reaction of the aminodiene (1) with dichloromaleic anhydride (6) in ether at 0°C leads directly to the acid (14) which can be isolated and fully characterised. Either by heating the acid (14) in toluene, or by reaction of the aminodiene (1) with dichloromaleic anhydride (6) in hot toluene dechlorodecarboxylation occurs and the diene (15) is isolated in good yield. In contrast reaction of the aminodiene (3) with dichloromaleic anhydride (6) proceeded directly to give the conjugated diene (16); an intermediate bicyclic acid could not be isolated. The inability to isolate such an intermediate is not surprising as the absence of alkyl substitution will facilitate dechlorodecarboxylation. However it is interesting to note from the examples in Table 1 that the presence of the alkyl substituent controls the formation of the nonconjugated dienes rather than isomerisation to the conjugated dienes. These examples establish a simple route to diversely functionalised hydroisoindoles based on the use of dichloromaleic anhydride.

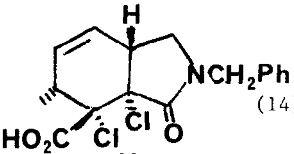
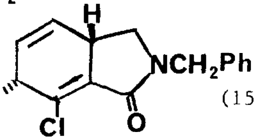
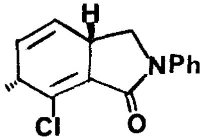
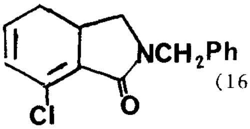
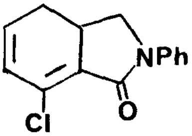
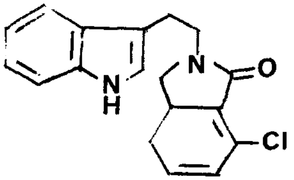


(1) $R^1=Me$; $R^2=CH_2Ph$
(2) $R^1=Me$; $R^2=Ph$
(3) $R^1=H$; $R^2=CH_2Ph$
(4) $R^1=H$; $R^2=Ph$
(5) $R^1=H$; $R^2=(3\text{-Indolyl})CH_2CH_2$



(10) $R^1=R^3=H$; $R^2=CO_2Me$
(11) $R^1=CO_2Me$; $R^2=R^3=H$
(12) $R^1=Br$; $R^2=CO_2Me$; $R^3=H$
(13) $R^1=R^3=Cl$; $R^2=CO_2Me$

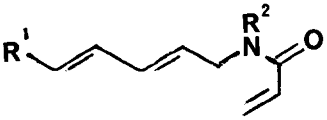
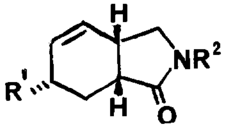
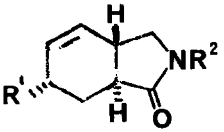
TABLE 1: Synthesis of Bicyclic Lactams from Dichloromaleic Anhydride

Aminodiene	Conditions	Products (% Yield[a])	
(1)	Et_2O; 0°C; 15 h	 (14)	69
(1)	PhMe;Δ ; 15 h	 (15)	91
(2)	PhMe;Δ ; 15 h		87
(3)	PhMe; Δ ; 15 h	 (16)	65
(4)	PhMe; Δ ; 15 h		58
(5)	PhMe; Δ ; 15 h		67

[a] Isolated yields after chromatography or by crystallisation.

In the first reports[7] of the use of the IMDA reaction in the synthesis of hydroisoindole the cis- or trans- nature of the ring junction was a focus of attention. It was recognised that the nature of the dienophilic moiety greatly influenced the observed stereoselectivity. Whereas acrylamides obtained by reaction with acryloyl chloride afforded cis- and trans-fused hydroisoindoles with little or no selectivity, functionalised acrylamides obtained by reaction with maleic anhydride or related dienophiles afforded predominantly trans-fused adducts.

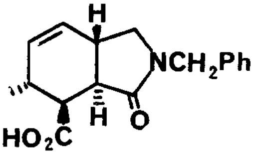
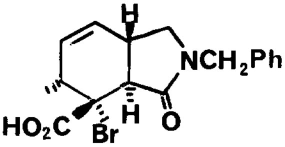
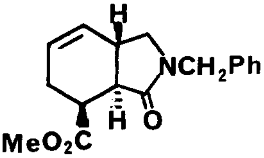
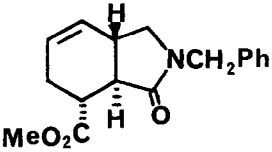
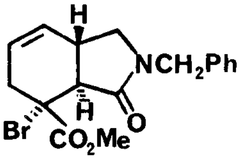
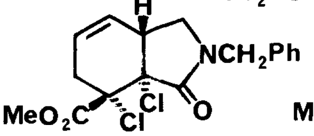
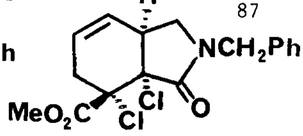
TABLE 2: Cyclisation of Amides Derived from Acryloyl Chloride

Amidotriene	Yield (%)[a]	Products (%)		Ratio (cis/trans)
				
R^1=H; R^2=Ph	71	42	29	3:2
R^1=Me; R^2=Ph	67	46	21	2:1
R^1=H; R^2=CH_2Ph	66 (100)[b]	32 (52)[b]	34 (48)[b]	1:1
R^1=Me; R^2=CH_2Ph	57	29	28	1:1
R^1=H; R^2=(3-Indolyl)CH_2CH_2	82	40	42	1:1

[a] Isolated yields after chromatographic separation.

[b] Reference 1: yield determined by hplc analysis.

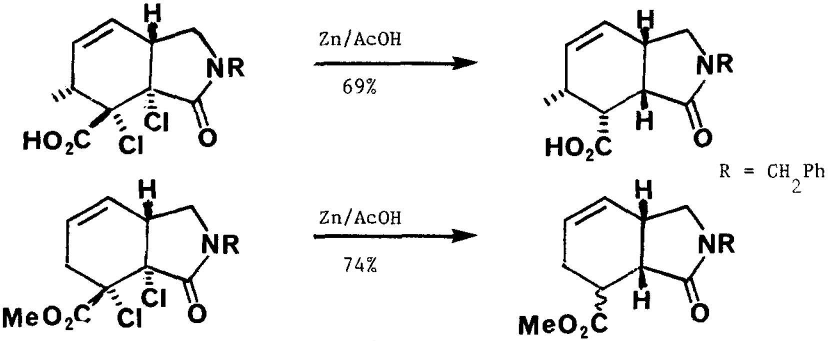
TABLE 3: Synthesis of Bicyclic lactams from other Dienophiles

Aminodiene	Dienophile	Products	(% Yield[a])
(1)	(8)		82
(1)	(9)		38
(3)	(10)		21
(3)	(11)		41
(3)	(12)		90
(3)	(13)	 	87

[a] Isolated yields after chromatographic separation.

In a study of the selectivity of addition of 11 variously substituted dienophiles, our results are shown together with the recent French result[1] with unsubstituted acrylamides, in Table 2, and with the diverse further functionalised acrylamides in Table 3. The unsubstituted acrylamides (Table 2) add with little selectivity, although it is interesting to note that this selectivity is influenced by the nature of the nitrogen substituent. The more functionalised acrylamides derived from the dienophiles (8-13) add to give uniquely the trans- adducts or in the case of (13) dominantly the trans-adduct. These results have two important implications. First by use of substituted maleic anhydrides and related esters the IMDA reaction can be used to give a variety of functionalised hydroisoindoles; the successful application to tryptamine derivatives highlights the possible use of these reactions in the synthesis of natural products.

Secondly a new route to cis-fused hydroisoindoles can be based on the adducts derived from dichloromaleic anhydride (6). As shown in the Scheme both acid and ester adducts are smoothly reduced by zinc in acetic acid to afford cis-fused hydroisoindoles. Hence the esters (10) and (11) afford trans-fused adducts whereas the routes based on the anhydride (6) or the ester (13) afford after reduction cis-fused adducts.



Scheme

References and Notes

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