Investigations Into The Stereochemical Outcome Of Intramolecular Diels-Alder Reactions

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Abstract

The Diels-Alder (DA) reaction is an important tool in synthetic organic chemistry, since it allows the simultaneous formation of two carbon-carbon (or carbon-heteroatom) bonds. The stereoselectivity of intramolecular versions of this reaction is, however, difficult to predict. A systematic study of the intramolecular Diels-Alder (IMDA) reaction has been carried out which provides new insights into factors affecting stereocontrol. Ester tethered substrates were chosen for this investigation because there are relatively few literature examples of this type and esterification provides a versatile way of attaching the diene to the dienophile.

Two chiral dienols were prepared and these were used to synthesize a range of precursors for investigating asymmetric induction in ester tethered DA (ETDA) reactions. When a stereogenic centre was incorporated into precursors at the allylic position to the diene terminus, high levels of π-facial stereoselectivity were observed. The amount of stereocontrol was dependent on the size of the stereocontrolling element that was used, but diastereoisomer ratios of up to 96:4:0:0 were achieved. This method of stereocontrol represents a powerful new method for achieving asymmetric induction in IMDA reactions. Conversely, no diastereofacial selectivity was observed when the ETDA precursor lacked a stereocentre at the allylic position.

The *endo:exo* and π-facial stereoselectivity of maleate and fumarate derivatives of the chiral dienols (and achiral examples prepared from (2*E*,4*E*)-2,4-hexadien-1-ol) were compared and an explanation of the observed stereoselectivity is proposed. For maleates there was a clear preference for *trans*-fused *exo* adducts, whether the dienophile was terminated with a carboxylic acid or a methyl ester group. In contrast to this, *cis*-fused *endo* adducts were favoured for chiral fumarate precursors, regardless of the type of functional group that the dienophile was terminated with. In each case the π-facial stereoselectivity was slightly greater for the ester than the corresponding carboxylic acid. These observations undermine previous literature reports which claim that the geometry of the dienophile is not a dominant factor in the *endo:exo* stereoselectivity of ETDA reactions. It is also counter to the view that carboxylic acids promote the formation of *endo* adducts, and esters promote *exo* adducts respectively.

Determination of the stereochemistry of the ETDA adducts was accomplished by taking into account the absolute stereochemistry of existing stereogenic centres in the precursors, COSY and NOESY spectra of the adducts, the coupling constants arising at the ring junction, and conformational analysis using molecular models. A tricyclic derivative was prepared from one of the ETDA adducts and nOe difference experiments were carried out on it, which confirmed the stereochemical assignments that were made. Preparation of this derivative serves as a model system for the syntheses of himbacine

(which is a lead compound in the treatment of Alzheimer's disease) and velutinal (a powerful antifeedant for the opossum), both of which possess a similar carbocyclic backbone to the tricycle that was formed.

The assertion that carboxylic acids form *endo* adducts in ETDA reactions has gone unchallenged for over twenty years. The most frequently cited evidence for this behaviour involves DA reactions of citraconate derivatives of (2*E*,4*E*)-2,4-hexadien-1-ol. Since the results obtained for a range of maleate half esters conflicted with the published results for citraconate half esters, a thorough reinvestigation of the literature examples was carried out. Each of the possible *exo* and *endo* DA adducts for the two regioisomeric (2*E*,4*E*)-2,4-hexadien-1-yl hydrogen citraconate precursors was prepared and characterized independently, to enable the products formed in the DA reactions to be identified by proton NMR analysis. It was demonstrated that (2*E*,4*E*)-2,4-hexadien-1-yl citraconate half esters are thermally labile and break down when heated in refluxing solvent to form citraconic anhydride and (2*E*,4*E*)-2,4-hexadien-1-ol. This impacts upon the commonly held belief that (2*E*,4*E*)-2,4-hexadien-1-yl citraconate half esters undergo *ETDA* reactions to form predominantly *endo* adducts. In fact, the experiments described herein demonstrate that the *endo* adducts form by way of *bimolecular* DA reactions between citraconate anhydride and (2*E*,4*E*)-2,4-hexadien-1-ol, which occur subsequent to cleavage of the ester tether. In reactions of other citraconate half esters (involving alcohols which are less volatile than (2*E*,4*E*)-2,4-hexadien-1-ol) it was possible to isolate the respective alcohols in yields of 54-63%.

Steroids are attractive synthetic targets, since rare examples of steroidal natural products with potent biological activity are regularly discovered. Practical synthesis of steroids *via* transannular Diels-Alder (TDA) reactions is an attractive strategy, since it should be accomplished by simply heating the starting material in an appropriate solvent (which can be subsequently recycled). A more ambitious approach involves the stereocontrolled tandem TDA reaction of a macrocycle containing a *bis*-diene (in the form of a conjugated tetraene) and a *bis*-dienophile. Such a reaction would involve the simultaneous formation of four carbon-carbon bonds and eight new stereogenic centres in a single step. A chiral tetraenol and a monoprotected dienedioic acid containing a *bis*-dienophile moiety have been prepared. Esterification of these materials and selective manipulation of the protecting groups was carried out, but macrocyclisation has yet to be achieved. Progress in this area has set the scene for tandem TDA reactions to be attempted.

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Cheers,

Mike.

"What have you lost Mulla?"

"My key," said Nasrudin.

"Where did you drop it?"

"At home."

"Then why, for heaven's sake, are you looking for it here?"

"There is more light here."

A Sufi Parable.

Contents

Abbreviations

%	percentage yield
Δ	heat
Ac	$-O_2CCH_3$
AIBN	2,2'-azo-*bis*-isobutyronitrile
APT	attached proton test
BDA	bimolecular Diels-Alder
BHT	2,6-di-*tert*-butyl-4-methylphenol
BMS	borane methyl sulphide complex
Bn	benzyl
°C	degree Celsius
ca	circa (approximately)
CA	citraconic anhydride
CI	chemical ionization
COSY	correlated spectroscopy
d	day/s or doublet/s
DA	Diels-Alder
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimde
DEPT	distortionless enhancement by polarization transfer
DMAP	N,N-diemthylaminopyridine
DMES	dimethylethylsilyl
DMF	dimethylformamide
DMP	dimethoxypropane
DIBALH	diisobutylaluminium hydride
DMSO	dimethylsulphoxide
EDG	electron donating group
EI	electron impact
endo	tether carbonyl distant from diene in the transition state
eq	molar equivalents
Et	ethyl
ETDA	ester tethered Diels-Alder
EWG	electron withdrawing group
eV	electron Volts
exo	tether carbonyl close to diene in transition state
h	hour/s
HETCOR	heteronuclear COSY

HMQC	heteronuclear multiple quantum correlation
HOMO	highest occupied molecular orbital
HSQC	heteronuclear single quantum correlation
IMDA	intramolecular Diels-Alder
imid.	imidazole
internal	carbon atom/bond close to tether
iPr	isopropyl
LUMO	lowest unoccupied molecular orbital
MA	maleic anhydride
Me	methyl
min	minute
MOM	methoxymethyl
NMR	nuclear magnetic resonance
nOe	nuclear Overhauser effect
NOESY	nuclear Overhauser and exchange spectroscopy
peripheral	carbon atom/bond distant from tether
Ph	phenyl
$PhCH_3$	toluene
PhH	benzene
Pip	piperonyl
PMB	*para*-methoxybenzyl
ppm	parts per million
pyr.	pyridine
q	quartet
ROESY	rotating frame Overhauser enhancement spectroscopy
RT	room temperature
s	singulet
t	time or triplet
T	temperature
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TDA	transannular Diels-Alder
TFA	trifluoroacetic acid
TfO	trifluoromethanesulphonate
TBDPS	*tert*-butyldiphenylsilyl
TEA	triethylamine
TIMDA	tandem intramolecular Diels-Alder
TIPS	triisopropylsilyl

TLC	thin layer chromatography
TMS	trimethylsilyl
xyl	xylene
$\chi\rho$	chiral group