Pergamon

Tetrahedron Letters, Vol. 38, No. 8, pp. 1463-1466, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00058-0

Diastereoselective Intramolecular Diels-Alder Reaction of the Furan Diene. A Facile Access to Enantiopure Epoxy Tetrahydroisoindolines.

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Abstract: 2-(2'-Furfuryl)-N-acryloyl tetrahydro-1,3-benzoxazine **2a** participates in diastereoselective intramolecular Diels-Alder reaction in very mild conditions leading to two diastereoisomeric *exo*-adducts with good diastereoselectivity. Chromatographic separation of both addits, and further elimination of the menthol appendage allows to prepare enantiopure *iso*-indoline derivatives in excellent chemical yields. © 1997 Elsevier Science Ltd. All rights reserved.

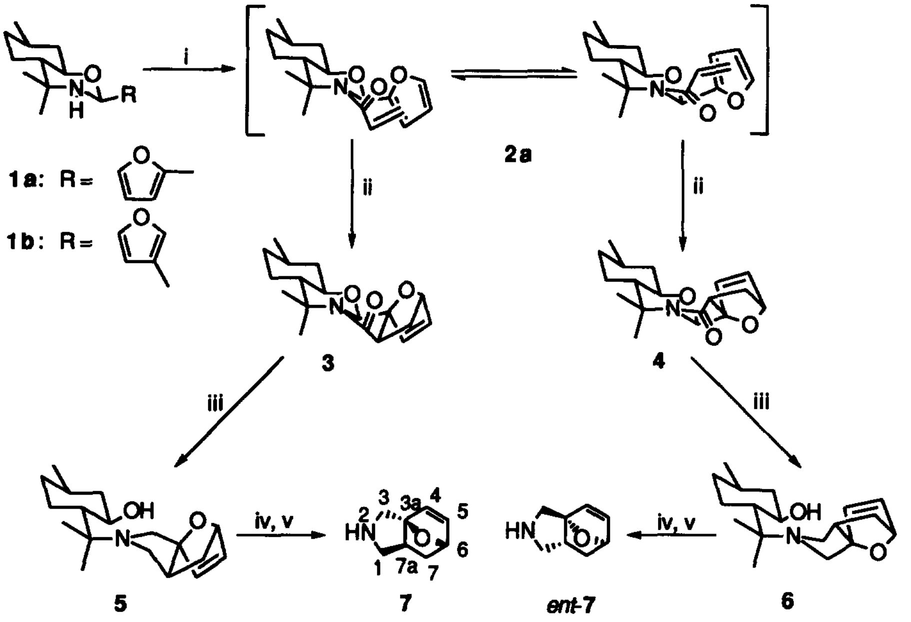
The synthesis of oxatricyclic γ-lactams is interesting because their potential transformation into usefull products.[1] To this end, intramolecular Diels-Alder reaction employing furan as the dienic component (IMDAF), including some diastereoselective approaches[1,2] have been used.[3] As a part of an ongoing projet directed to the use of chiral tetrahydro-1,3-oxazines in asymmetric synthesis,[4] we present here a diastereoselective IMDAF reaction using this heterocycle as chiral template, and directed to the preparation of *iso*indoline derivatives.

To this end, chiral tetrahydro-1,3-benzoxazines **1a-b** were prepared as single diastereoisomers,[5] by condensation of (-)-8-aminomenthol[6] with 2-furaldehyde and 3-furaldehyde respectively, in benzene at R.T. in 96% chemical yield.

The dienophile component was introduced by reaction of **1a-b** in CH_2Cl_2 with acryloyl cloride in the presence of triethylamine at 0°C. In these conditions the acrylamide **2b** can be isolated,[7] but **2a**[8] immediately participates in the IMDAF reaction leading to a mixture of two diasteroisomeric cycloadducts **3** and **4** in a 71:29 ratio, in 88% total chemical yield. (Scheme 1).

Contrary to previously described for tertiary amides,[9] the stereoselectivity of the reaction was deeply affected by the nature of the solvent,[2] and some results are collected in Table 1. These data indicate that the cycloaddition does not occur below 0°C (entry 1 in the Table), and that the temperature only has a little effect on the ratio of diastereoisomers (copare entries 2 and 3 or 5 and 6). On the contrary, the change from CH_2Cl_2 to hexane as solvent just inverts the ratio of stereoisomers at the same temperature (compare entry 3 versus 8 in the

Table). Compound **4** was also formed as major diastereoisomer when the solvents of the reaction were diethyl ether or toluene, but the diastereomeric excess highly decreased; in clorobenzene the major diastereoisomer



Scheme 1: *Reagents and conditions*: i) $CH_2{=}CHCOCl$, NEt_3, 0°C, 15-30 min. ii) Solvent, Time, Temperature (Table 1), chromatographic separation. iii) AlH_3, THF, -10°C, 5 min. iv) PCC, 4Å mol. sieves , R.T., 6 h. v) 2.5M KOH in THF-MeOH, R.T., 5h.

Table 1. IMDAF reactions of **2a** in different solvents.

Entry	Solvent	Time (H)	T (ºC)	Yield (%)[a]	Diast. Ratio[b] 3 / 4
1	CH_2Cl_2	720	-10	---	---
2	CH_2Cl_2	190	0	88	71 / 29
3	CH_2Cl_2	15	23	96	69 / 31
4	Et_2O	18	20	73	45 / 55
5	$C_6H_5CH_3$	190	0	93	37 / 63
6	$C_6H_5CH_3$	14	23	96	38 / 62
7	$C_6H_5CH_3$	3	110	93	43 / 57
8	Hexane	15	23	96	22 / 78
9	C_6H_5Cl	215	0	89	53 / 47

[a] Yields refer to pure compounds after column chromatography. [b] Diastereomeric ratios were measured by ^1H-NMR in the reaction mixtures.

formed was **3**, but the diastereoselection was very low. It is noteworthing that the acrylamide **2b** derived from 3-furaldehyde does not participate in the IMDAF reaction, and it was recovered unchanged after heating for 24 h in decalin at reflux.

The diastereoisomers **3** and **4** were easily isolated as pure compounds[10] by column chromatography (silica gel EtOAc: hexane 1:3) and, after recrystallization, they were converted into the amino alcohols **5** and **6** respectively by reduction[11] with AlH_3 in THF at -10°C, in 93% chemical yield. The crude reaction mixture of **5** was transformed into **7** ($[\alpha]_D^{25}$ = +30.31 (c = 5.6, CH_2Cl_2) by sequential PCC oxidation in the presence of 4Å molecular sieves and retro-Michael reaction by treatment with a 2.5M solution of KOH in THF-MeOH.[12] The same sequence over **6** led to *ent*-**7** ($[\alpha]_D^{25}$ = -30.12 (c = 2.1, CH_2Cl_2).

The absolute configuration of **7** was stablished by X-ray crytallography of **3**[13] (Figure 1) and was shown to be (3aS, 6S, 7aS), whereas the assignement of the absolute stereochemistry for *ent*-**7** was made by comparison of the sign and value of the specific rotation with those measured for **7**.

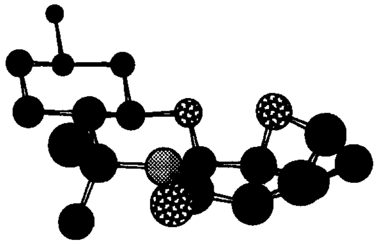


Figure 1. Chem 3D of compound **3** from X-ray coordinates

The observed stereochemical results can be interpreted by accepting that the approach of the furan nucleus to the dienophile occurs with an *exo* orientation, as previously stated for IMDAF reactions when the linkage betwen both components is short.[2,14] Otherwise, the transition state leading to **3** has a net dipole moment about the amide bond, and consequently must be stabilized by solvents with higher dielectric constants, whereas the less polar transition state yielding **4** is favored in non-polar solvents.[9a, 15]

It is worthy to note that the major diastereoisomer **3** obtained in CH_2Cl_2 was the kinetically controlled product, because after isolation, it was transformed into the thermodynamically more stable **4** (**4**/**3**: 75/25) by refluxing for 24 h. in decalin.

Because the cleavage of the oxanorbornene system is a well documented process,[16] the described reaction opens a way to a diversity of enantiopure compounds, and efforts are in progress to further study the applications of this reaction, that will be reported in due course.

Acknowledgements: The authors thank the Spanish DGICYT (Projects PB92-0262 and PB95-0707) for financial support of this work. One of us (J. N.) thanks the Spanish Ministerio de Educación y Ciencia for a predoctoral Grant (P. F. P. I.).

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7. **2b** : Colorless solid, m.p. 61-62°C (from EtOH). $[\alpha]_D^{25}$ = +18.45 (c = 1, CH_2Cl_2). ^{1}H-NMR: 7.46 (m, 1H); 7.34 (m, 1H); 6.45 (m, 1H); 5.33 (s, 1H); 3.54 (dt, 1H, J_1 = 10.6 Hz, J_2 = 4.2 Hz); 1.96 (m, 1H); 1.65-1.77 (m, 2H); 1.48 (m, 1H); 1.15 (s, 3H); 1.11 (s, 3H); 0.93 (d, 3H, J = 6.6Hz). ^{13}C-NMR: 142.9; 139.5; 126.5; 108.6; 78.3; 75.1; 51.5; 51.4; 41.6; 35.0; 31.4; 29.9; 25.6; 22.3; 19.6.
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13. Crystal data for compound **3**: $C_{18}H_{25}NO_3$. Mr=303.40, tetragonal, space group P 4_12_12, a = 12.950(2) Å, b = 12.950(2)Å, c = 19.142(5)Å, V= 3210(1) Å^3, Z = 8, D_x = 1.26/cm^3. MoK_α radiation (graphite crystal monochromator, λ = 0.71073 Å), μ (MoK_α) = 0.791 cm^{-1}, F(000) = 1312, T= 200K. Final conventional R-factor = 0.028 for 2182 'observed' reflections and 299 variables. The structure was solved by Direct Methods using SHELXS86.
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(*Received in UK* 17 *December* 1996; *accepted* 10 *January* 1997)