INTRAMOLECULAR VERSUS INTERMOLECULAR DIELS-ALDER REACTION IN THE CYCLISATION REACTION OF FURFURYL AMINES WITH MALEIC ANHYDRIDE

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Abstract: The mechanism of the reaction between various N- substituted furfuryl amines and maleic anhydride was re-investigated and fully elucidated. The reaction proceeds by condensation of the amino group on the anhydride function followed by an intramolecular Diels-Alder reaction. In one case the intermediate compound was isolated and fully characterized for the first time.

Introduction:

Intramolecular Diels-Alder (IMDA) reactions of furan derivatives offer a very fruitful entry to the synthesis of substituted heterocycles (1, 2, 3, 4, 5). In connection with a work directed to the synthesis of optically active γ lactams (figure **1**) we re-examined the mechanism of the cyclization of furfuryl amines with maleic anhydride and the structure of the adduct for which two different stereoisomers have been proposed (6, 7).

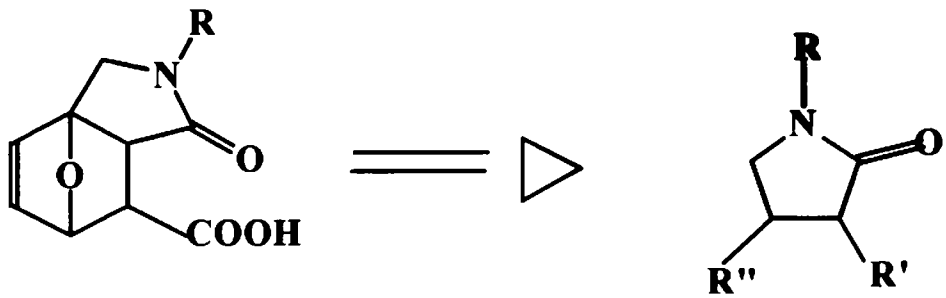
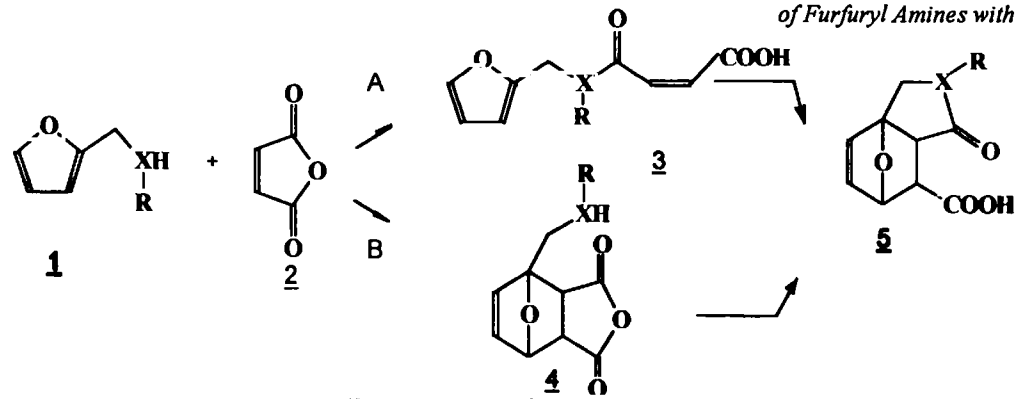


Figure **1:** Retro synthetic pathway for substituted γ lactams

Two different pathways may account for the cyclization reaction (figure **2**):

- condensation of the amine 1 with maleic anhydride 2, followed by an IMDA reaction (path A)
- intermolecular Diels-Alder reaction (NDA) of the furan nucleus with 2, followed by an intramolecular attack of the amino group on the anhydride function (path B).



Compounds	R	X	RX
a	$CH(CH_3)_2$	N	-
b	$CH(CH_3)C_6H_5$	N	-
c	C_6H_5	N	-
d	-	-	O

Figure **2:** IMDA versus NDA reaction for the cyclisation of furan derivatives with maleic anhydride

In a previous study path A was proposed (6) for 1c, with the intermediate formation of 3c characterized by IR spectroscopy (strong absorption band at 1020 cm^{-1}: furan nucleus) and by its melting point (88-89 °C) different from that of 5c. However in preliminary experiments we characterized the ammonium salt of 1c with maleic acid , which was present as an impurity in 2, and which shows characteristics very similar to those reported for 3c. Furthermore contradictory results were reported for the very similar reaction of furfuryl alcohols with 2 (8, 9):

- formation of the product 4d isolated and fully characterized by NMR and IR which could be further converted to 5d by traces of moisture (path B). The product 3d prepared independently was also shown to cyclize into 5d in 40% yield (8)
- formation of 5d via path A with characterization of 3d which crystallized along with 5d when the amount of solvent was exceedingly minimized (9).

Results:

Faced with these results we re-examined the reaction of furfuryl amines (1a-c) with maleic anhydride under various conditions.

At room temperature, without solvent, 1a reacts with 2 (1 to 1 ratio) in a few minutes, to yield 5a in 93% yield. When the reaction is performed in acetone, chloroform, toluene, ether or ethyl acetate, 5a is also formed as the only product, although in a lower yield (65%). However in all these solvent the reaction is very fast and is over in five minutes and no intermediate can be detected even when the reaction is performed in an NMR tube (10).

When reacting equimolar ratio of racemic 1b and 2, the tricyclic product 5b is isolated in good yield. An NMR study in $(CD_3)_2CO$ solution shows that the reaction is complete within five minutes;

however spectra indicate the presence of more than one product. More detailed examination of the reaction with optically pure 1b (R or S) permitted to establish that the two products formed in each case are diastereomeric acids. The latter are isolated in the pure form as methyl esters. When dissolved in DMSO-d_6 each ester slowly equilibrates, on standing, into a 40:60 mixture of the two isomers. The equilibration can be explained by a retro Diels-Alder reaction compatible with path A. However no intermediate such as 3b, could be detected by NMR studies at room temperature in the early stage of the reaction.

More clear cut results are obtained with amine 1c. By following the reaction by NMR we observe the fast formation of 5c in $(CD_3)_2CO$ (5 min) while the reaction takes about 30 min in $CDCl_3$ or in DMSO-d_6. However in all these solvents we observe transient signals centered at 5.00 and 6.09 ppm in $(CD_3)_2CO$ or 4.96 and 6.10 ppm in $CDCl_3$. These signals disappear while those characteristic of 5c become evident. When the reaction is performed in an IR-FT cell we observe the fast disappearance of the two characteristic absorption bands of 2 (1794,1863 cm^{-1}) while two new ones appear at 1725 and 1632 cm^{-1}. These absorptions then decrease while absorption bands at 1716 and 1697 cm^{-1} appear, indicating the formation of 5c. The two transient bands at 1725 and 1632 cm^{-1} and the two signals in ^1H NMR can be assigned to compound 3c which can be isolated in a pure form. Indeed when the reaction is performed at -10°C in diethyl ether, 3c precipitates and can be recovered in 80% yield. It has been fully characterized by IR, ^1H and ^{13}C NMR (11). The IMDA cyclization of 3c into 5c is total and can be followed by ^1H NMR (half time in $(CD_3)_2CO$: 30 min; in $CDCl_3$: 90 min and several months in the solid phase at 5°C).

Adducts 5a, 5b and 5c all have the same relative configuration around the two newly formed C-C bonds, the carboxylic group and the C-C bond of the γ lactam are exo as it was previously reported by Bilovic (6). This relative configuration can be easily deduced from ^1H NMR spectra. The coupling constant between the two endo hydrogen atoms is 9 ppm, a value which is in full agreement with published data (6) and Karplus correlation's (12). Furthermore the structure has been confirmed by X ray analysis of 5c (figure 3).

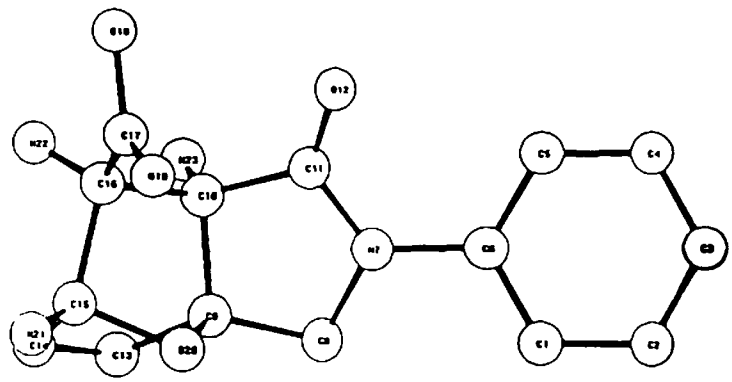


Figure 3: X Ray structure of 5c

Conclusion:

For the first time the exact mechanism of the reaction between furfuryl amines and maleic anhydride has been demonstrated. The intermediate compound has been isolated in one case and fully characterized, and its behaviour to undergo an IMDA reaction was shown by an NMR study. Such a cyclisation mechanism opens the way to control of diastereoselectivity and this is now further explored in our laboratory.

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(10) All the reactions performed in an NMR tube, were achieved using a 0.5M solution of amine and a 0.5M solution of maleic anhydride (1/1).

(11) NMR spectroscopic data for 5a, 3c and 5c are reported for $CDCl_3$ solutions. δ are given in ppm relatively to that of tetramethyl silane. Satisfactory elemental analysis were obtained for these compounds.

5a : NMR: ^1H: 6.50, s, 2H; 5.29, s, 1H; 4.38, sept., J=6.6Hz, 1 H; 3.9, d, J=12Hz, 1H; 3.76, d, J=12Hz, 1H; 2.93, d, J=9.1Hz, 1H; 2.83, d, J=9.1Hz, 1H; 1.18, t, J=6Hz, 3H.

^{13}C: 173.1, 172.0, 137.4, 135.0, 106.2, 60.3, 51.25, 49.9, 49.2, 48.2, 45.3, 14.26.

3c: NMR: ^1H: 7.44, m, 4H; 7.37, m, 2H; 6.31, d, J=3,1Hz, 1H; 6.24, d, J=3,1Hz,1H; 6.16, s, 2H; 4.97, s, 2H.

^{13}C: 166.0, 165.0, 148.4, 142.8, 139.8, 136.1, 130.2, 129.5, 128.6, 127.6, 110.6, 110.4, 46.6.

5c : NMR: ^1H:(methyl ester): 7.58, d, 2H; 7.36, t, 2H; 7.15, t, 1H; 6.58, d, J=5.7Hz; 6.48, d, J=5.7hz; 5.20, s, 2H; 4.43, d, J=11.5Hz, 2H; 4.20, d, J=11.5Hz, 2H; 3.80, s, 3H; 2.99, d, J=9Hz, 2H; 2.83, d, J=9Hz, 2H.

^{13}C: 172.2, 170.0, 139.1, 137.2, 135.2, 128.9, 124.9, 120.4, 87.6, 81.6, 52.3, 52.2, 50.0, 45.5.

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