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Unexpected Rearrangement of Intramolecular Diels-Alder Adducts of Citraconic Anhydride and Secondary Furfuryl Amines

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Abstract:

The intramolecular Diels-Alder reactions of citraconic anhydride with several secondary furfuryl amines have been studied at different temperatures. At high temperatures, only a single cycloadduct was isolated, whilst at room temperature, a mixture of two regioisomeric adducts were formed. One of the regioisomers rearranged to another when heated in a solvent. Some aspects of the mechanism were investigated.

Keywords: Diels-Alder reaction; Citraconic anhydride; Furfuryl amines; Rearrangement.

The intramolecular Diels-Alder reactions of furans continue to be an active area of research with several natural product syntheses being achieved employing this reaction [1]. One of the advantages is that even sterically hindered and less reactive dienophiles can be made to react [2]. The outcome of such reactions greatly depends on the tether connecting the furan and dienophile and generally alkyl substitutions on the tether facilitate cycloaddition [3]. We reasoned that by appropriate choice of the tether, cycloaddition between furan and citraconic anhydride (**1**) - a reaction that takes place only under high pressure, could be achieved under normal conditions [4]. We are interested in this reaction as it provides direct access to new derivatives of Palasonin (a potent inhibitor of protein kinases that stimulate cell proliferation [5]). In addition, these cycloadducts may also be useful CD-ring intermediates in the synthesis of paclitaxel analogues [6]. In this article, we describe the results of our studies employing an amino group as a linker between the furan unit and **1**.

The reaction between unsubstituted furfuryl amine and **1** produced a mixture of citraconamic acids and they did not undergo cycloaddition even under high pressure conditions. Similar results have been reported for the reaction between furfuryl amine and maleic anhydride [7]. We then examined secondary furfuryl amines. When **1** was treated with amines (**2-9**) in benzene solution at reflux, cycloadducts (**10-17**) were obtained in high yields (**Scheme -1**). The stereo- and regiochemistry of the adduct **10** was determined by 2D NOESY experiments. The methyl protons (δ1.23) showed cross peaks with H-3 (δ2.39), H-6 (δ6.38), H-7 (δ3.68) and the aromatic protons. The H-3 proton showed cross peaks with methyl, H-4 (δ5.22) and H-5 (δ6.56) protons and no cross peaks with either H-7 or aromatic protons[8]. The observed cross

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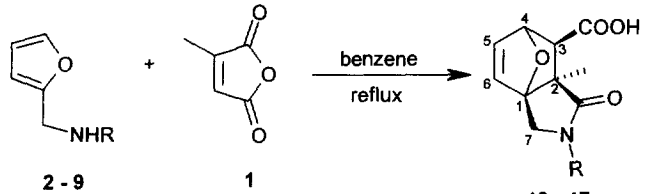
peaks clearly show that the adduct has an *exo* configuration since, in the *endo* isomer the methyl would be on the *exo* face and point away from the ring and therefore would not show any NOESY cross peaks with the olefinic protons. The identities of the products **11** – **17** were established from the same chemical shift pattern as for compound **10**. It is notable that ring opening of the anhydride and cycloaddition have taken place regio- and stereoselectively with the methyl group and furfuryl side chain adjacent to one another in this unsymmetrical system. It is also important to mention that high pressure is not necessary to achieve cylcoaddition between citraconic anhydride and a furfuryl amine. The results are presented in the following table.

Scheme – 1

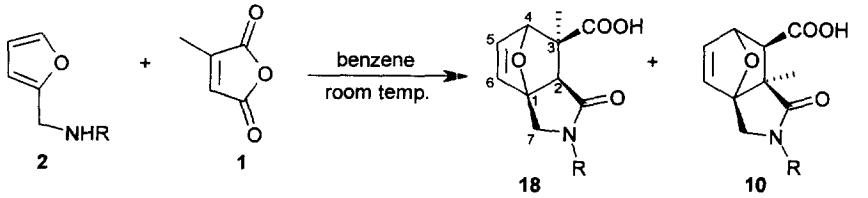


2 - 9 **1** **10 - 17**

Amine	R	Product	Yield(%)
2	Benzyl	**10**	84
3	2-methylbenzyl	**11**	70
4	2-hydroxybenzyl	**12**	83
5	2-methoxybenzyl	**13**	66
6	4-methoxybenzyl	**14**	87
7	4-nitrobenzyl	**15**	57
8	2-naphthylmethyl	**16**	77
9	Cyclohexyl	**17**	76

When the reaction of **1** and **2** was performed at 0°, only ring opening of **1** was observed. At room temperature, the reaction between **1** and **2** provided a white precipitate in about 30% yield after several hours. Absence of furan protons and presence of signals at δ1.33 and δ2.46 in the NMR spectrum indicated it to be a cycloadduct but one different from **10**. The structure was established with the help of NOESY data. The methyl protons showed cross peaks with H-2 (δ2.46), H-4 (δ5.30) and the olefinic protons (δ6.50). On the other hand, the H-2 proton showed cross peaks with methyl, olefinic and H-7 (δ3.82) protons. Based on these observations, we assigned the new cycloadduct as **18**, which is a regio isomer of adduct **10** [9]. We further examined the reaction mixture owing to the poor yield of **18**. It revealed that in addition to **18**, adduct **10** was also present in substantial amounts (**Scheme – 2**).

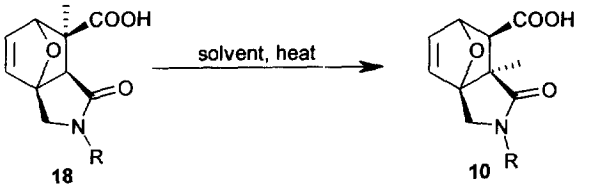
Scheme – 2



2 **1** **18** **10**

Surprisingly, upon attempted crystallisation from ethyl acetate, **18** completely rearranged to **10**. The initial reaction mixture containing both the adducts was converted into **10** upon heating. Amines **3-9** also provided a mixture of cycloadducts at room temperature and they all rearranged to single adducts when heated in a solvent (**Scheme – 3**). Thus, the cycloadducts undergo regioisomerisation with the application of heat. To the best of our knowledge, this kind of regioisomerisation has not been observed in an intra molecular Diels-Alder reaction before[10].

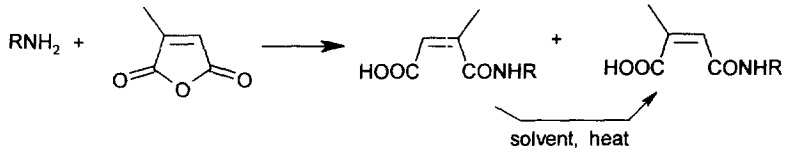
Scheme – 3



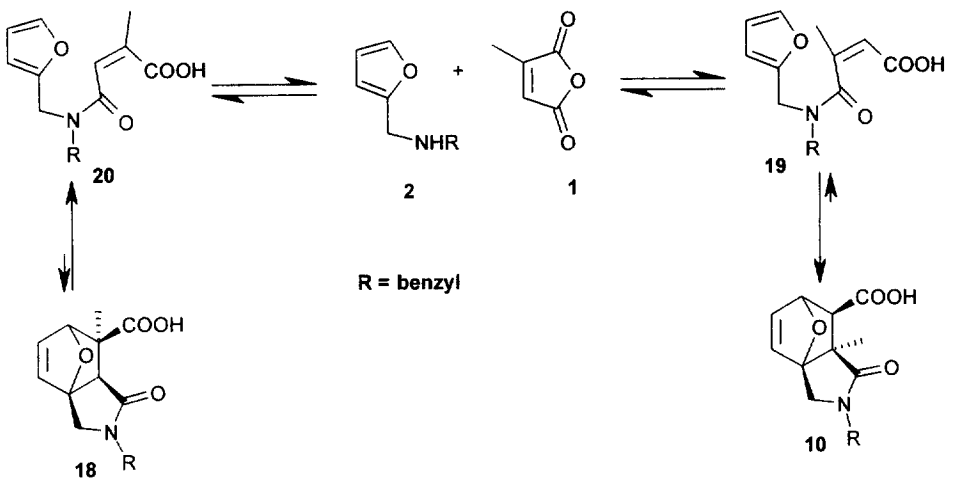
18 10

The reaction of citraconic anhydride (**1**) with amines has been studied in the past[11]. Amines attack both carbonyls of the anhydride leading to mixtures of citraconamic acids. Interestingly, the mixture could be rearranged into a single product by heating in a solvent. In that case, the final product contained the methyl group at the carboxylic acid end. This is in contrast to our observations with furfuryl amines, where the amino group is attached to the carbonyl containing the methyl group (**Scheme -4**).

Scheme - 4



Intrigued by the contrasting results, we monitored the reaction between **1** and **2** by NMR spectroscopy. Observations made over two weeks led to the following conclusions. Opening of **1** by the amine is non-selective and reversible as indicated by the easily identified methyl signals of the amic acids **19** and **20** at δ2.06 and δ2.18 and those belonging to **1** (δ2.25). We also observed the formation of **19, 20** and **1**, when **18** was heated in benzene for a short time (15min). Citraconamic acids **19** and **20** then cyclise to **10** and **18** respectively. We noticed that the signal at δ1.33 (methyl group of **18**) decreased with time while that at δ1.23 (methyl group of **10**) increased and after two weeks **10** was almost exclusively present in the solution. This can be explained by considering that **18** is reversibly formed from **20**, which is in equilibrium with **1** and **2**. Thus, **18** itself is in equilibrium with the starting compounds via **20**. Formation of **10** from **19** is effectively irreversible as shown by its increase in proportion with time. The equilibrium between **19** and the starting compounds is altered drastically because of this and it lies almost to the side of **19**. This indicates that **10** is the thermodynamically most stable compound in this mixture. Thus, the indirect equilibrium between **19** and **20** can be rationalised. These equilibria are accelerated by the application of heat and as a result **10** is isolated as the sole product at higher temperatures. While, it is not clear why **10** is thermodynamically preferred over **18,** the results obtained show that formation of a Diels-Alder adduct clearly outweighs the thermodynamic preferences of the ring opening of the anhydride by the amine.



In conclusion, we have shown that selectivity of the Diels - Alder reaction between furfuryl amines and **1** can be altered by the application of heat. Efforts are currently underway to transform these highly functionalised cycloadducts into biologically active analogues of Palasonin.

References and Notes:

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[8] NMR data for compound **10**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36-7.22 (m, 5H, Ar), 6.55 (dd, J=5.7, 1.6Hz, 1H, H-6), 6.38 (d, J=5.7Hz, 1H, H-5), 5.22 (d, J=1.5Hz, 1H, H-4), 4.73 (d, J=14.9Hz, 1H, benzylic), 4.33 (d, J= 14.9Hz, 1H, benzylic), 3.65(AB quartet, J=11.9Hz, 2H, H-7, H-7'), 2.39 (s, 1H, H-3), 1.23 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 75MHz): 175.6, 174.1, 137.7, 135.7, 133.1, 128.9, 128.0, 127.8, 91.0, 81.7, 56.4, 53.7, 47.0, 46.8, 21.8 ppm.

[9] NMR data for compound **18**: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.36–7.23 (m, 5H, Ar), 6.53-6.48 (m, 2H, H-5, H-6), 5.3 (d, J=1.1Hz, 1H, H-4), 4.54 (AB quartet, J=14.8Hz, 2H, benzylic), 3.82 (d, J=12.1Hz, 1H, H-7), 3.62 (d, J=12.1Hz, 1H, H-7'), 2,46 (s, 1H, H-2), 1.33 (s, 3H, Me); ^{13}C NMR ($CDCl_3$, 75MHz): 174.8, 172.6, 136.1, 135.4, 135.2, 129.0, 128.2, 128.1, 89.7, 85.7, 58.2, 53.3, 48.8, 47.1, 23.6 ppm.

[10] In a related reaction, diastereomeric Diels-Alder adducts of a chiral furfuryl amine and maleic anhydride were found to equilibrate in solution. See: Zylber J, Tubul A, Brun P. Tetrahedron: Asymmetry 1995;6:377-380.

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