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Synthesis of Polysubstituted Anilines Using the Diels-Alder Reaction of Methyl 5-Aminofuroate

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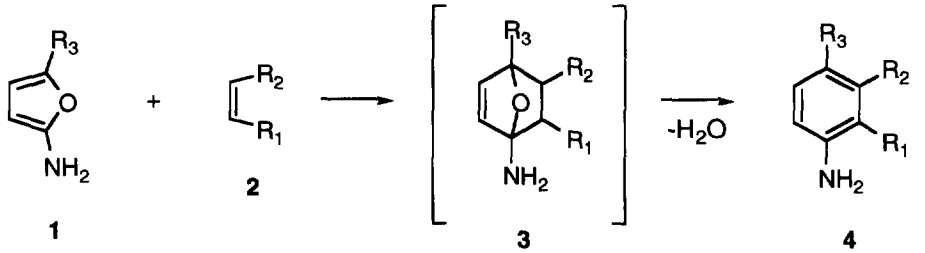
Abstract: *Methyl 5-aminofuroate undergoes a facile [4+2]-cycloaddition with a variety of dienophiles to afford ring opened cycloadducts which are readily dehydrated using BF_3·OEt_2 to give polysubstituted anilines.* Copyright © 1996 Elsevier Science Ltd

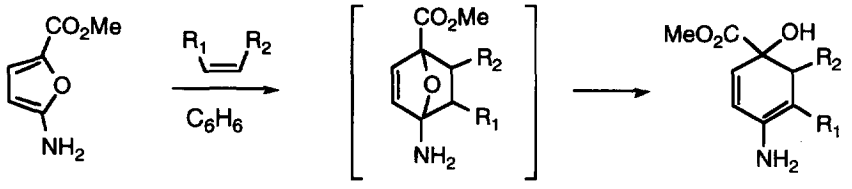
Substituted anilines are important starting materials for the preparation of heterocyclic compounds and pharmaceuticals.[1-3] Notable examples of biologically active molecules containing derivatized anilines in their structure include antibiotics,[4] analgesics[5] and β-adrenergic blockers.[6] Anilines are also key intermediates in the synthesis of a variety of aromatic compounds *via* diazotization[7] and nucleophilic substitution reactions.[8] Conventional methods for the synthesis of anilines include the reduction of nitroaromatics,[9] nucleophilic aromatic substitution[10] and the rearrangement of aryl carboxylic acid derivatives.[11] These methods suffer from the drawback that a benzene ring that contains most of the requisite functionality must be used as the starting material for the reaction. A more practical route to anilines involves the condensation of two acyclic precursors to form the polysubstituted aromatic ring.[12] From our recent work dealing with the Pummerer-promoted formation of α-amino isobenzo-furans,[13] we have become interested in the Diels-Alder reaction of 2-aminofurans as a method for preparing substituted aniline derivatives. The details of this new cycloaddition reaction are the subject of this communication.



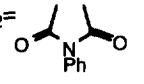
There are only a few cases in the literature where [4+2]-cycloadditions of 2-aminofurans have been investigated.[14] The paucity of examples is undoubtedly due to the inaccessibility and inherent instability of the 2-aminofuran ring system.[15] Several groups have attempted to synthesize 2-aminofuran but have failed to isolate the parent compound due to its lability.[16] Addition of electron withdrawing groups to the

furanamine nucleus is known to enhance its stability.[15] These *stable* furanamines participate in [4+2]-cycloaddition chemistry but the examples reported to date produce products that do not contain useful substitution patterns.[14] The furanamine ester **5**, first reported by Freure and Johnson,[17] is known to exhibit typical enamine behavior,[18] but there have been no reports dealing with its cycloaddition chemistry. The Diels-Alder reaction of **5** with various dipolarophiles should afford amino-substituted 7-oxabicyclo[2.2.1]heptenes (**3**) which are expected to spontaneously ring-open to produce substituted anilines of type **4**. This reaction would constitute a general route into polysubstituted anilines. Furthermore, the product contains an ester group which can be removed *via* hydrolysis and decarboxylation, which allows for a wide range of target molecules.

Methyl 5-nitrofuroate was synthesized by a slight modification of the literature procedure.[17] Catalytic reduction using palladium on calcium carbonate afforded furanamine **5** in 63% overall yield. Heating a sample of **5** with various dienophiles in refluxing benzene for 12 h afforded the rearranged cycloadduct **7** in high yield.[19] In each case, the cycloaddition proceeded with high regioselectivity,

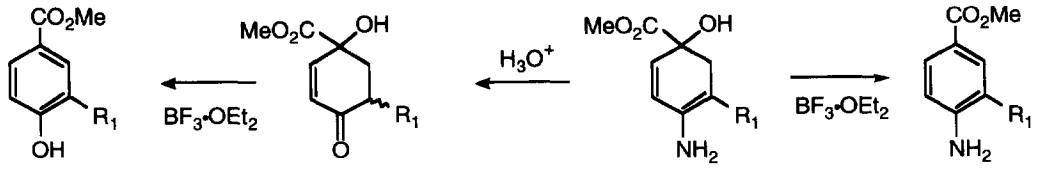


5 **6**

7a; R_1=CO_2Me; R_2=H; 92%
7b; R_1=CN; R_2=H; 99%
7c; R_1=SO_2Ph; R_2=H; 78%
7d; R_1=COMe; R_2=H; 74%
7e; R_1=R_2=CO_2Me; 80%
7f; R_1=CO_2Me; R_2=Me; 68%
(3:2-mixture of diastereomers)
7g; R_1=R_2= 

with the electron-withdrawing group R_1 being located *ortho* to the amino functionality. The regiochemical results are perfectly consistent with FMO theory. The most favorable FMO interaction is between the HOMO of the furanamine and the LUMO of the dienophile. The atomic coefficient at the ester carbon of the furan is larger than at the amino center and this nicely accommodates the observed regioselectivity.[20,21]

Subjection of the initially formed cycloadducts **7** to an equivalent of BF_3•OEt_2 in benzene at 80°C for *ca* 1 h resulted in smooth dehydration to give the polysubstituted aniline system **8a-8d** in excellent yield. When **7** was exposed to an aqueous THF solution containing a trace of *p*-TsOH at 25°C for 30 min, it was



10a (94%)
10c (84%)
10d (92%)

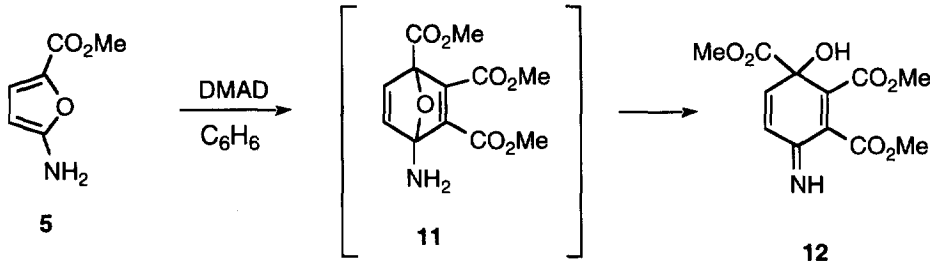
9a (84%)
9c (74%)
9d (82%)

7

8a (96%)
8b (99%)
8c (84%)
8d (74%)

smoothly converted to the corresponding cyclohexenones **9**. Further treatment of **9** with BF_3•OEt_2 afforded the related phenols **10** in *ca* 80% yield

The reaction of **5** with dimethyl acetylenedicarboxylate did not give the expected cycloadduct **11** but instead afforded the ring-opened product **12**. Thus, heating a sample of **5** with DMAD in benzene afforded imine **12** in 58% isolated yield. The structure of **12** was assigned on the basis of its characteristic spectral data [^{1}H-NMR ($CDCl_3$, 300 MHz) δ 3.74 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.27 (s, 1H), 5.27 (s, 1H), 6.37 (d, 1H, J=10.2 Hz), 6.78 (d, 1H, J=10.2 Hz)].[19]



5

11

12

In summary, the [4+2]-cycloaddition of methyl 5-aminofuroate proceeds with a variety of dienophiles to afford ring-opened cycloadducts which can readily be converted to polysubstituted anilines. Further application of the method to intramolecular cycloadditions is currently under investigation and will be reported on at a later date.

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