

## Cycloadditions of 3-Amino-2H-1,4-oxazin-2-ones with Olefins: Generation of 5,6-Dihydro-2-oxo-2H-pyran-6-carbonitriles.

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**Key Words:** *Diels-Alder reaction; ring transformation; 3-amino-2H-1,4-oxazin-2-ones; 2H-pyran-6-carbonitriles; 5-amino-2,4-pentadienenitriles.*

**Abstract:** *The Diels-Alder adducts from the reaction of 3-amino-2H-1,4-oxazin-2-ones 1b-d with olefins in toluene at reflux, undergo ring transformations yielding previously unknown 5,6-dihydro-2-oxo-2H-pyran-6-carbonitriles 3. In some cases the latter are converted into 5-amino-2,4-pentadienenitriles 4. A plausible mechanism is proposed.*

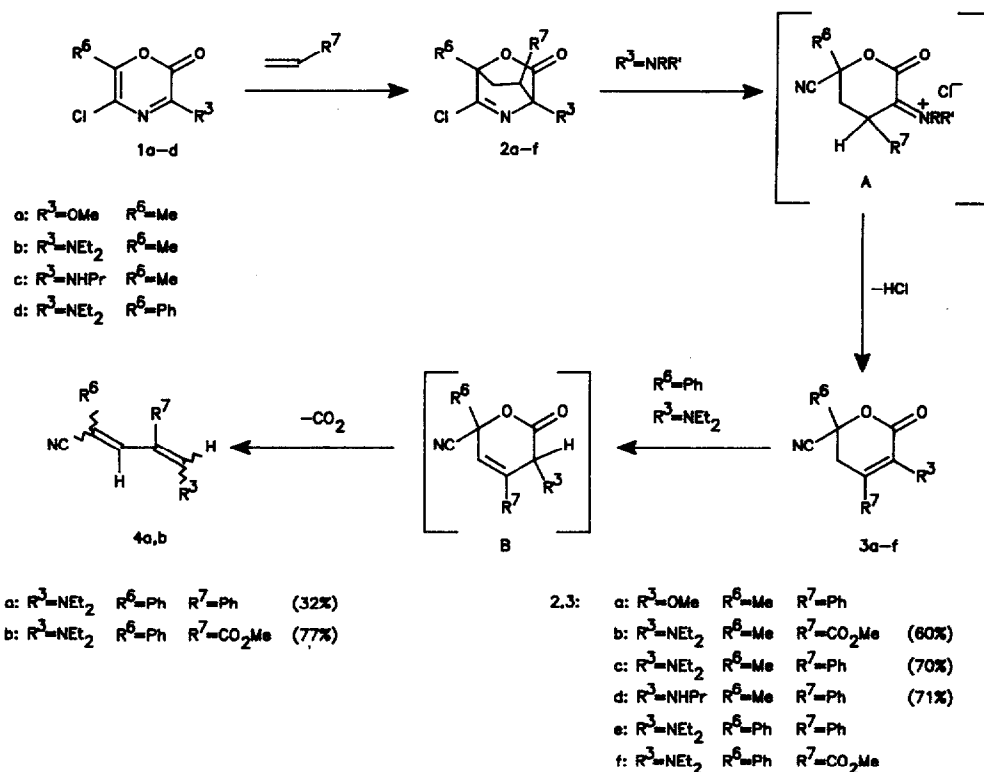
The Diels-Alder activity of the 2-azadiene system has been studied in several heterocycles.<sup>1</sup> Usually the cycloadditions are carried out with acetylenic compounds affording pyridines as is the case with 3,5-dichloro-2H-1,4-oxazin-2-ones.<sup>2</sup>

In parallel work<sup>3</sup> we investigated the Diels-Alder reaction of the 2-azadiene system in these 3,5-dichloro-2H-1,4-oxazin-2-ones 1 ( $R^3=Cl$ ,  $R^6=H$ , alkyl, aryl) with olefins ( $R^7=H, Ph, CO_2R...$ ) yielding 2-oxa-5-azabicyclo[2.2.2]oct-5-en-3-ones of type 2. The reaction was shown to be rather general: when reacting with ethene, oxazinones 1 with a methoxy or tolyl group in position 3 or with various substituents in position 6 also gave compounds of type 2 ( $R^7=H$ ). On heating, these compounds did not lose  $CO_2$  by a retro Diels-Alder reaction observed for the adducts with acetylenic dienophiles<sup>2b</sup> and for adducts of 6H-1,3-oxazin-6-ones with alkenes.<sup>4</sup>

Now we report our peculiar results (Scheme 1) observed in the reaction of olefins with 3-amino-5-chloro-2H-1,4-oxazin-2-ones 1b-d obtained from the corresponding 3,5-dichloro compounds.<sup>5</sup> In the cycloaddition of the model oxazinone 1b (2.3 mmol) with three equivalents of methyl acrylate (3 h in 5 ml of toluene at reflux), a yellow product was isolated (60%) after chromatography (silica gel, 5% EtOAc/ $CHCl_3$ ) of the evaporated reaction mixture. It had not the expected structure of 2b ( $R^3=NEt_2$ ,  $R^6=Me$ ,  $R^7=CO_2Me$ ) neither of the hydrolysed product. In the  $^1H$  NMR spectrum for these structures, three multiplets should appear for the diastereotopic protons<sup>3</sup> on the bridge. However we found two doublets at 2.79 ppm and 3.02 ppm ( $^2J=17.6Hz$ ) in  $CDCl_3$  as solvent. The proton coupled  $^{13}C$  NMR spectrum of the obtained compound showed the coupling of a carbon atom with two protons ( $^1J=135Hz$ ) and the coupling of another carbon atom with the protons of a methyl ( $^2J=5Hz$ ) and a methylene group ( $^2J=5Hz$  and  $2.5Hz$ ).

Also the presence of a nitrile function coupled with a methyl ( $^3J=5\text{Hz}$ ) and a methylene group ( $^3J=10\text{Hz}$  and  $2\text{Hz}$ ) was observed. In the IR spectrum the nitrile absorption was lacking but two carbonyl absorptions appeared at  $1700\text{ cm}^{-1}$  and  $1750\text{ cm}^{-1}$ . Based on the NMR and mass spectral data (absence of chlorine;  $M^+$  calculated: 266.1262, found: 266.1265) the structure of methyl 6-cyano-3-diethylamino-5,6-dihydro-6-methyl-2-oxo-2H-pyran-4-carboxylate **3b** was assigned to the yellow oil.

With regard to the mechanism (Scheme 1) we believe that the originally formed compound **2b** undergoes a C-N cleavage assisted by the nitrogen lone pair at the bridgehead position; a comparable expulsion of  $\text{Cl}^-$  as observed for adducts with alkynes<sup>6</sup> should yield intermediate **A**; loss of the acidic proton in position 4 eventually leads to the identified compound **3b**.



Scheme 1

In further experiments we studied the possible influence of the dienophile and of the substituents  $R^3$  and  $R^6$  of the starting 2H-1,4-oxazin-2-one **1**. The cycloaddition of oxazinone **1b** with three equivalents of styrene (3 hours in toluene at reflux) gave a 70% yield of a yellow crystalline product, identified as 3-diethylamino-5,6-dihydro-6-methyl-2-oxo-4-phenyl-2H-pyran-6-carbonitrile **3c**. In the proton NMR spectrum of **3c** the diethylamino group is observed as a triplet at 0.96 ppm (Me) and as two quartet x doublet absorptions at 2.90 ppm ( $\text{CH}_2$ ) as in the case of **3b**. The methylene group next to the chiral center absorbs as two doublets at 2.92 ppm and 3.27 ppm ( $^2J=17\text{Hz}$ ) whereas the phenyl protons appear at about 7.4 ppm.

Compound **3c** could be recrystallized from *n*-hexane (mp: 89°C) and showed correct combustion analytical data (Calcd for  $C_{17}H_{20}N_2O_2$ : C, 71.81; H, 7.09; N, 9.85. Found: C, 71.77; H, 7.13; N, 9.84).

Cycloaddition of the 2*H*-1,4-oxazin-2-one **1a** ( $R^3=OMe$ ,  $R^6=Me$ ) with styrene yielded only adduct **2a** with the characteristic  $^1H$  NMR absorptions for the ethylene bridge protons. Probably the electron donating effect of the methoxy group is not strong enough to induce a C-N cleavage as observed for the 3-diethylamino substituent.

Reaction of oxazinone **1c** (diethylamino group in position 3 replaced by a propylamino group) with styrene for 5h, under the same conditions as described above, yielded again a yellow crystalline product **3d** (mp: 50°C). Its  $^{13}C$  NMR data and other spectral data resemble those of **3c**.

In contrast with the previous results, the addition of styrene to the oxazinone **1d** did not yield the 2-oxo-2*H*-pyran-6-carbonitrile **3e**. The  $^1H$  NMR spectrum of the new yellow compound obtained after reaction for one day did not show any methylene group (except for those of the diethylamino group) but two additional protons in the aromatic region of the spectrum. A nitrile IR absorption at 2200  $cm^{-1}$  but no lactone absorption (at about 1740  $cm^{-1}$ ) was observed. The mass spectrum showed a molecular ion, 44 unities lower than expected for compound **3e**. Considering these data and the intense yellow colour of the product a structure with an extra double bond conjugation is proposed. Comparison of the  $^{13}C$  NMR spectrum with those of structures known in the literature<sup>7</sup> [**4c** ( $R^3=NHMe$ ,  $R^6=R^7=H$ ) and **4d** ( $R^3=NHMe$ ,  $R^6=Me$ ,  $R^7=H$ )] allowed to assign the structure of 5-diethylamino-2,4-diphenyl-2,4-pentadienenitrile **4a** with still unknown configuration. The product was recrystallized from hexane/ether (95°C) and showed correct combustion analytical data (Calcd for  $C_{21}H_{22}N_2$ : C, 83.40; H, 7.33; N, 9.26. Found: C, 82.89; H, 7.42; N, 9.18).

In order to test further application of the latter reaction with oxazinone **1d**, we performed the cycloaddition with methyl acrylate. The yellow crystalline product (77%) (mp: 67°C) isolated after reaction for 4 h had not structure **3f**. Based on its spectral data that correspond with those of **4a**, it was identified as the 4-cyano-2-(diethylaminomethylene)-4-phenyl-3-butenolate **4b**.

For the mechanism (Scheme 1) we suppose that the initially formed 2-oxo-2*H*-pyran-6-carbonitrile **3** undergoes a 1,3-proton shift to yield intermediate **B** that then loses carbon dioxide by a retro Diels Alder reaction to form the 2,4-pentadienenitrile **4**. In order to prove the intermediation of compounds **3e-f** we tried to isolate **3f** by working at lower temperatures.

When the reaction of oxazinone **1d** with methyl acrylate was carried out at 70°C, a TLC spot with a  $R_f$  value higher than for the pentadienenitrile **4b** was observed after reaction for 1-3 hours. Later on the product disappeared and after complete reaction only the pentadienenitrile **4b** was left. Repeating this reaction and stopping it after 3 hours yielded a mixture of starting oxazinone **1d**, pentadienenitrile **4b** and the presumed intermediate. The latter was isolated by using fast column chromatography on silica gel (5% EtOAc/ $CHCl_3$ ) and characterized as the carboxylate **3f** by its  $^1H$  NMR spectrum. This spectrum corresponds to those of other compounds of type **3**: signals for the diethylamino group at 1.1 ppm and 3.3 ppm and two doublets for the methylene group appearing at about 3.3 ppm. However the compound was not stable even at room temperature and it was shown to be easily converted into **4b**.

In conclusion we can state that an easy way is opened for previously unknown 5,6-dihydro-2-oxo-2H-pyran-6-carbonitriles some of which are converted into 5-amino-2,4-pentadienenitriles by a 1,3-proton shift and subsequent retro Diels-Alder reaction. These pentadienenitriles are potentially useful as intermediates for cardiovascular agents.<sup>8</sup> Synthetic approaches for suchlike structures have already been reported and can be subdivided into two groups: the photolytic,<sup>9</sup> nucleophilic<sup>7,10</sup> or base induced<sup>11</sup> ring opening of pyridine(derivatives) or benzodiazepines and nucleophilic substitution<sup>12</sup> or addition<sup>13</sup> processes on open chain systems. The general application of the method generating 5,6-dihydro-2-oxo-2H-pyran-6-carbonitriles, the factors determining their conversion into 5-amino-2,4-pentadienenitriles and the configuration of the latter are under current investigation.

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