JOC *Note*

Synthesis of Highly Substituted Aniline and *o*-Phenylenediamine Derivatives Containing Various Substitution Patterns

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Abstract: The Diels−Alder reactions of a variety of 2*H*-pyran-2-ones **1** with alkynes **2** yielding highly substituted aniline and *o*-phenylenediamine derivatives **4** with novel (and in some cases known but very rare and useful) structural patterns are presented. The effect of substituents of both reactants on the reaction rates was investigated. The reactions were carried out under thermal conditions, as well as at high pressures.

The Diels−Alder reaction[1] of various dienophiles with 2*H*-pyran-2-ones[2] represents an important tool in organic synthesis. There have been many reports on cycloadditions of alkynes with 2*H*-pyran-2-ones, beginning with Alder and Rickert[3] in 1937 and continuing with a plethora of articles.[4,5] Such reaction results in the construction of various substituted benzene systems, which could otherwise only be obtained through lengthy synthetic sequences. This reaction is usually regioselective and compatible with many functionalities (thus minimizing the need for protection groups) and in many cases takes place in the absence of a catalyst. Besides the well-established dienophiles,[4] such as electron-poor acetylene carboxylates, where the Diels−Alder reaction with a normal electron demand usually takes place, there are also reactions starting from electron-rich phenyl-substituted acetylene[4g,h] and even more electron-rich *N*,*N*-diethyl-1-propyn-1-amine as a dienophile,[5] where the inverse electron-demand Diels−Alder reaction seems to take place.[6]

Aromatic amines are very important compounds, being the structural units of some medicinally important molecules and many other industrially relevant materials.[7] The amino function can be introduced into the benzene ring by a wide variety of methods, i.e., by the reduction of a nitro moiety, by the replacement of a halogen atom, by rearrangement reactions, etc.[7a,b] Different anilines have also been obtained by the amination of arenes with azodicarboxylates, followed by the reduction of the primary-formed hydrazino intermediates,[7c,d] by the Buchwald−Hartwig cross-coupling reaction,[7e−g] by the microwave-assisted replacement of a halogen atom with the amino moiety,[7h] etc.

2*H*-Pyran-2-ones with electron-donating groups attached to position 3 are mentioned in the literature only occasionally as substrates for the Diels−Alder reaction. Namely, there have been reports starting from 3-alkyl-,[4g,h,j,k] 3-hydroxy-,[4h] and 3-methoxy-2*H*-pyran-2-ones.[4g,h] To our knowledge no reaction was described starting from 3-amino- or derivatized 3-amino-2*H*-pyran-2-ones. Our experiences with such 2*H*-pyran-2-ones and their fused derivatives have shown that they are very useful substrates for the Diels−Alder reaction with alkenes (maleic anhydride[8a] and maleimides[8b]) to give products containing new structural patterns of substituents. These results prompted us to perform cycloaddition reactions with various alkynes in order to obtain novel types of benzene derivatives as well as some already known.

Here we report on cycloadditions of 3-benzoylamino-2*H*-pyran-2-ones **1a**−**d**,[9] with a variety of alkynes **2a**−**e** as dienophiles. Compounds **1a**−**d** also contain a weak electron-donating substituent at position 6 and an electron-withdrawing group at the position 5. Upon the cycload-

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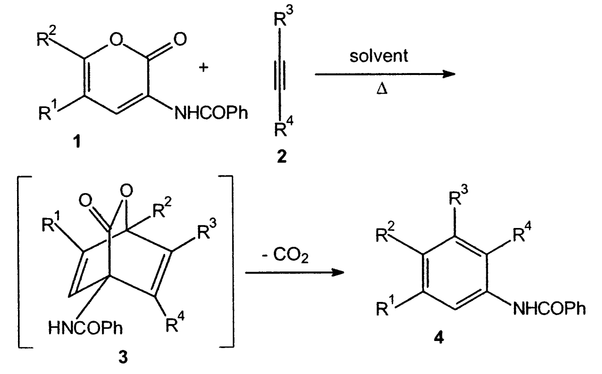
SCHEME 1



dition reaction and the spontaneous elimination of carbon dioxide from the intermediate **3**, we isolated multifunctional, highly substituted aniline **4a**–**l** and *o*-phenylenediamine derivatives **4m**,**n** (Scheme 1, Table 1).

We investigated the reactions under thermal as well as under high-pressure conditions (13–15 kbar). The thermal reactions were preliminarily conducted in various solvents, including dichloromethane, tetrahydrofuran, toluene, decalin, tetralin, and water. We also tried to accelerate the reactions by using a variety of Lewis acids ($ZrCl_4$, $AlCl_3$, $SnCl_4$, $BF_3{\cdot}Et_2O$) and some metal oxides (Al_2O_3, CuO, Fe_2O_3, PtO_2, TiO_2, ZnO). We did not observe any catalytic effect with the first group of compounds when applied in tetralin; only in the presence of $ZrCl_4$ were the corresponding products formed (**4c** from **1a** and **2c**, as well as **4f** from **1b** and **2b**) after the same reaction times and with the same yield and regioselectivity, whereas all of the others seemed to disable the alkynes or 2*H*-pyran-2-ones for further reaction. The metal oxides, on the other hand, did not change the reaction times, the regioselectivity, or the yield of the reactions, when employed for the synthesis of **4b** from **1a** and **2b** in tetralin. In these experiments we found that the best yields for the alkynes **2a**–**d** were obtained using the solvent with the highest boiling point, which in our case was tetralin. In decalin, for example, within the same reaction time a conversion toward **4b** lower than that in tetralin was observed (after 3 h, 77% vs 91% conversion). Since we were not able to avoid the application of high-boiling-point tetralin by means of a catalyst, we decided to try to accelerate our reactions by employing increased pressure. The high-pressure technique[10] has often been used in synthesis, including transformations starting from 2*H*-pyran-2-ones and alkenes but very seldom (in fact, in just one case) with alkynes.[11] Having in mind that CO_2-containing adducts obtained by the cycloaddition of alkenes on 2*H*-pyran-2-ones (namely, bicyclo[2.2.2]octene systems) can be isolated[10c,11] in certain cases (especially under high-pressure reaction conditions), we were curious to check the possibility of detecting the very unstable, not yet isolated, intermediary-formed bicyclo[2.2.2]octa-1,4-diene system under very mild reaction conditions. All the high-pressure reactions were carried out in dichloromethane (or in a few cases in methanol) at room temperature and at pressures of 13–15 kbar (Table 1). Our investigations showed that some reactions were successful and gave products **4** in acceptable yields. This was the case when starting from **1b** and some acetylenes (runs 5–7), but we did not detect any of the bicyclo[2.2.2]octa-1,4-diene representatives.

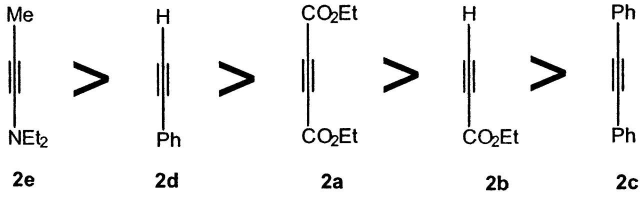


FIGURE 1. Relative dienophile reactivity toward **1a**.

In contrast to the electron-deficient alkynes **2a**,**b** and phenyl-substituted alkynes **2c**,**d**, ynamine **2e** showed the greatest reactivity toward our 2*H*-pyran-2-ones, and its reactions were completed in 30 min at room temperature in dichloromethane solutions. Its regioselective cycloaddition produced highly substituted *o*-phenylenediamine derivatives **4m**,**n**.

To gain more insight into the progress of the reaction, we decided to stop the reactions of alkynes **2a**–**d** after a short reaction time (1.5 h). After evaporating the solvent and analyzing the crude mixtures of products using ^1H NMR spectroscopy, we obtained the results presented in Table 1. In the case of run 2 we separated the reaction mixture and isolated product **4b** in 24% yield; unreacted starting **1a** was recovered in 63% yield.

Because the reaction of the 5-acetyl-2*H*-pyran-2-one derivative **1a** with *N*,*N*-diethyl-1-propyn-1-amine (**2e**) took place in dichloromethane at room temperature and on the basis of the products distributions after 1.5 h (Table 1), we can postulate the relative order of dienophile reactivity toward **1a**, as shown in Figure 1. This order of reactivity is the opposite to that described for the transformations of a variety of 2*H*-pyran-2-ones with phenylacetylene and methyl propinoate (the latter being more reactive).[4g] On the other hand, the same order of reactivity of alkynes was observed for the Diels–Alder reactions with 3,6-bis(3,4-dimethoxybenzoyl)-1,2,4,5-tetrazines.[12] Similarly, we investigated the influence of substituents for other selected 2*H*-pyran-2-ones **1b**–**d** on the reaction rates with dienophiles **2a**–**d** and found the same reactivity order as in the case of **1a**. We also reacted a mixture of two 2*H*-pyran-2-ones **1a** and **1c** with one dienophile **2** (**2a** and **2d**, respectively), as well as a mixture of two dienophiles **2b** and **2d** with one 2*H*-pyran-2-one **1** (**1a** and **1c**, respectively) and established the mass balance for these two cases. In all examples we obtained results very similar to those presented in Table 1.

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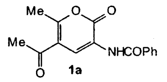
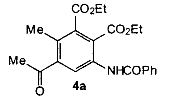
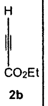
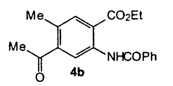
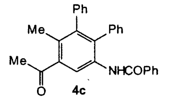
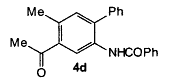
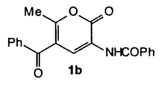
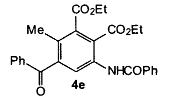
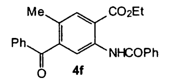
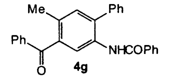
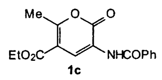
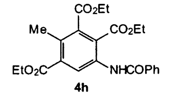
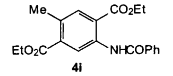
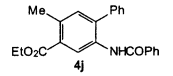
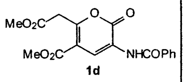
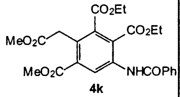
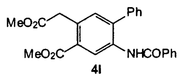
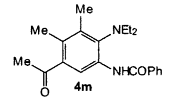
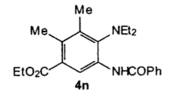
TABLE 1. Reaction Times, Products Distributions, and Yields of Products 4

run	starting compounds		product	thermal			high pressure	
	1	**2**	**4**	t (h)	yield (%)[a]	prod. distr.[b]	t (h)[c]	prod. distr.[d] (yield, %)[a]
1	 **1a**	 **2a**	 **4a**	5[e]	67	**1a** : **4a** = 0.2 : 1	120	**1a** : **4a** = 1 : 0.1
2	**1a**	 **2b**	 **4b**	7.5[e]	94	**1a** : **4b** = 1 : 0.4	384	**1a** : **4b** = 1 : 0.15
				7.5[e,f]	90			
3	**1a**	 **2c**	 **4c**	12[e]	62	**1a** : **4c** = 1 : 0.2	528	**1a** : **4c** = 1 : 0
				12[e,g]	64			
4	**1a**	 **2d**	 **4d**	1[e]	98	**1a** : **4d** = 0 : 1	120	**1a** : **4d** = 1 : 0.3
5	 **1b**	**2a**	 **4e**	5[e]	74	**1b** : **4e** = 0.8 : 1	336	**1b** : **4e** = 0 : 1 (87)
6	**1b**	**2b**	 **4f**	9.75[g]	66	**1b** : **4f** = 1 : 0.2	384	**1b** : **4f** = 0.15 : 1 (70)
				9.75[e,g]	65			
7	**1b**	**2d**	 **4g**	1.75[e]	88	**1b** : **4g** = 0.1 : 1	336	**1b** : **4g** = 0 : 1 (91)
8	 **1c**	**2a**	 **4h**	6[e]	75	**1c** : **4h** = 1 : 0.7	168	**1c** : **4h** = 1 : 0.02
9	**1c**	**2b**	 **4i**	11.5[e]	82	**1c** : **4i** = 1 : 0.1	168	**1c** : **4i** = 1 : 0.02
10	**1c**	**2d**	 **4j**	6[e]	96	**1c** : **4j** = 0.3 : 1	144	**1c** : **4j** = 1 : 0.2
11	 **1d**	**2a**	 **4k**	6[e]	78	**1d** : **4k** = 1 : 0.5	312	**1d** : **4k** = 1 : 0
12	**1d**	**2d**	 **4l**	6[e]	76	**1d** : **4l** = 0.2 : 1	312	**1d** : **4l** = 1 : 0.3
13	**1a**	 **2e**	 **4m**	0.5[h]	95			
14	**1c**	**2e**	 **4n**	0.5[h]	79			

[a] Yield of isolated compounds. [b] Molar ratio estimated from ^{1}H NMR spectra of the crude reaction mixtures after 1.5 h (accuracy ≈ ±5%). [c] At 13–15 kbar in CH_2Cl_2 at room temperature. [d] Molar ratio estimated from ^{1}H NMR spectra of the crude reaction mixtures after high-pressure reactions (accuracy ≈ ±5%). [e] Tetralin as a solvent. [f] Addition of 10 mol % PtO_2. [g] Addition of 10 mol % $ZrCl_4$. [h] In CH_2Cl_2 at room temperature.

The influence of a substituent on the electron demand of 2*H*-pyran-2-ones directly corresponds with its influence on the activation or deactivation of the benzene ring toward aromatic electrophilic substitution.[13] On this basis it is reasonable to expect a weaker electron-donating power (nucleophilicity)[6d] for a 2*H*-pyran-2-one derivative containing more electron-withdrawing groups,[14] i.e., the 5-ethoxycarbonyl-2*H*-pyran-2-one derivative **1c** should be more nucleophilic (less electrophilic) than the 5-acetyl derivative **1a**. On the other hand, one would not expect a big change in the global nucleophilicity/electrophilicity power due to the presence of the 6-(methoxycarbonyl)-methyl moiety in compound **1d** in comparison with the 6-methyl group in compound **1c**. From the reactions of phenylacetylene with 2*H*-pyran-2-ones **1a**, **1c**, and **1d** it is evident that an electron-withdrawing substituent on 2*H*-pyran-2-one accelerates the reaction (**1a** is more reactive than **1c**; whereas **1c** and **1d** have approximately the same reactivity). From the results presented in Table 1 (products distributions after 1.5 h), we can conclude the following general reactivity order in the 2*H*-pyran-2-one series (with all dienophiles): **1a** > **1b** > **1c** ≈ **1d**. Finally, diphenylacetylene is the least reactive, probably as a result of huge stereoelectronic influences between the bulky phenyl group and the group at position 6.

Under high-pressure reaction conditions the reactivity cannot be estimated as easily because of the general inability to monitor the progress of the reaction. Many parameters might be responsible for the substantially higher reactivity of **1b** in comparison with other 2*H*-pyran-2-ones. The benzoyl group might exhibit different influences on activation and/or reaction volumes[10,15] than the acetyl or ethoxycarbonyl moiety. This might cause the change of the packing characteristics under high-pressure conditions and consequently different reactivity patterns. On the other hand, the problems associated with the solubility of reactants, especially at increased pressures, might also be responsible for the low conversion. Besides the standard solvent, dichloromethane, which readily dissolved our reagents at ambient pressures, we also tried methanol (in the synthesis of **4d** from **1a** and **2d**), but there was no appreciable effect on the yield of the reaction (168 h, **1a**:**4d** = 1:0.3). Accordingly, it is necessary to point out that the high pressure decelerates the elimination of CO$_2$ from the intermediate, thus allowing the adducts to equilibrate with the starting compounds in a retro-Diels−Alder reaction, and as a consequence lower product yields can be obtained.

The cycloaddition of unsymmetrically substituted alkynes **2b**,**d**,**e** regioselectively leads to just one type of products, as was clearly shown by TLCs and also by the ^{1}H NMR spectra of the crude reaction mixtures. The products obtained with **2b**,**d** (**4b**,**d**,**f**,**g**,**i**,**j**,**l**) had the 1,4 arrangement of protons (3-H and 6-H) on the benzene ring. These structures were proved on the basis of their ^{1}H NMR spectra, where for 3-H and/or 6-H protons only singlet signals appeared, consistent with the smallest coupling constants existing between the 1,4 arranged protons on the benzene rings ($J = 0-1$ Hz). The structures **4b**,**f**,**g**,**j** were further corroborated, with the HMBC spectra showing the correlation between 5-Me and 6-H (this correlation should not appear if the regioselectivity would be reversed). The structure of **4l** was proven on the basis of the NOESY spectrum, where a correlation between the CH$_2$ fragment and the 6-H was observed, as well as one between the NH and the 3-H. For the addition of **2e**, the NOESY spectrum of adduct **4n** shows Me-Me and NEt$_2$-NH correlations, which prove our proposed structures.

A detailed explanation of the observed regioselectivity cannot be given on the basis of our experiments. It might reflect the prevailing directing effect of the substituents on the 2*H*-pyran-2-ones **1**. In a similar way, though with lower regioselectivity, 3-methoxy-2*H*-pyran-2-one reacted with methyl propinoate and phenylacetylene.[4g] In our 3-benzoylamino-2*H*-pyran-2-ones, the hyperconjugative and/or steric effects of the 6-methyl substituents in conjunction with a strong electron-withdrawing influence of the 5-acyl (or 5-ethoxycarbonyl) moiety might contribute to the formation of single isomers. A detailed FMO analysis[4j] might give an additional explanation of the observed regioselectivity.

We would like to emphasize that we have produced multifunctionally substituted aniline and *o*-phenylenediamine derivatives **4**. Some of them seem to contain novel substitution patterns, whereas some other types have been already described in a few cases: 5-acyl-2-ester- (**4b**,**f**);[16] 5-acyl-2-phenyl- (**4d**,**g**);[17] 2,5-diester- (**4i**),[18] and 5-ester-2-phenyl- (**4j**)[19] substituted anilines.

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Supporting Information Available: Experimental Section; characterization data for all synthesized compounds (**4a**−**n**); and ^{13}C NMR spectra for compounds **4c**,**e**,**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

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