

An intermolecular Diels-Alder cycloaddition under various condition between 1,3-cyclohexadiene and 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate

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Abstract: The reaction between 1,3-cyclohexadiene and dimethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate both without a catalyst and with different catalysts, in both atmospheric and at high pressure, over 20 days were studied. At the end of the reactions, different products (*retro* Diels-Alder addition product **5** and Diels-Alder addition product **6**) were obtained in different yields. When we look at the percentage of the addition product, it is observed that the yield of reaction at high pressure in water is the highest. All structures of these products were characterized by ¹H-NMR, ¹³C-NMR, MS, and IR spectroscopy.

Keywords: Green chemistry; Diels-Alder reactions; catalyst; tetracyclicmolecule. ©2017 ACG Publications. All rights reserved.

1. Introduction

The Diels-Alder reaction is very important in terms of constructing simple and complex molecules and it has been widely used to make rings and bicyclic compounds for more than 80 years.¹⁻⁷ Cycloaddition occurs readily if the diene is substituted with electron-donating groups (as -OR, -NR₂, etc.), and the dienophile is substituted with electron-withdrawing groups (as -NO₂, -CN, -COR, etc.) or if one of them can be easily removed or consumed in a subsequent reaction.⁸ The Diels-Alder reaction can be reversible; this reaction is called the *retro* Diels-Alder reaction and is used to synthesize strained, interesting olefins.⁹⁻¹³ Heterocyclic and polycyclic molecules obtained via Diels-Alder or *retro* Diels-Alder reactions are very important in organic chemistry and they are used as starting materials in the pharmacology and other fields. In our recent studies, we reported the reaction between 2,3-dimethyl-1,3-butadiene and dimethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate with catalysts, i.e. phenol, acetic acid, nafion, and β-cyclodextrin.¹⁴ In the present study, we extended the Diels-Alder reaction between 1,3-cyclohexadiene (**4**) and dimethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**3**) with different catalysts (phenol, acetic acid, nafion, β-cyclodextrin) and also without a catalyst at 25 and 55 °C (Figure 1). Furthermore, this addition reaction was studied at different temperatures (25 and 55 °C) high pressure in water. (Table 1). There are examples of Diels-Alder studies in water in the literature.^{15,16} This is important for green chemistry.

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2. Experimental

2.1. Materials and Apparatus

Melting points were determined with a Mettler Toledo MP90 melting point system and were not corrected. Infrared spectra were recorded on a Perkin Elmer Win First® Satellite. The ^1H and ^{13}C NMR spectra were recorded on a Bruker Ultrashield Plus Biospin GmbH 400 MHz spectrometer. All chemical shifts (δ) were reported in ppm from internal TMS. Column chromatography was performed on silica gel (Kiesel-gel 60, 230-400 mesh, Merck). TLC was carried out on Merck 0.2 mm silica gel 60 F₂₅₄ analytical aluminum plates.

2.2. Synthesis of Dimethyl 7-oxo-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**3**)

Dimethyl 7-oxo-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**3**) was prepared as described in the literature.¹⁷⁻¹⁹

2.3. General Procedure for the Cycloaddition Reaction with Different Catalysts and Without Catalysts

Dienophile **3** (0.5 g, 2.4 mmol) and 1,3-cyclohexadiene (**4**) (0.197 g, 2.4 mmol) were dissolved in 10 mL of chloroform, and then the reaction was stirred at room temperature for 20 days. After the reaction, the solvent was removed. Then, the mixture of the products and starting molecules was separated with chromatography on 50 g of silica gel eluting with ethyl acetate/hexane (1:3). At the end of the purification *retro*-Diels Alder product **5** and addition product **6** were obtained. 10 mg of catalyst was added to the reaction medium in the catalyzed experiments.

(1*R*,4*S*)-dimethyl bicyclo[2.2.2]octa-2,5-diene-2,3-dicarboxylate (**5**)²⁰: Colorless oil. ^1H NMR (400 MHz, CDCl_3): δ = 6.31 (s, 2H), 3.96 (s, 2H), 3.7 (s, 6H), 1.41 (AA' part of AA'BB' system, quasi d, J = 6.8 Hz, 2H), 1.33 B part of AB system (BB' part of AA'BB' system, quasi, d J = 6.8 Hz, 2H) ^{13}C NMR (100 MHz, CDCl_3): δ = 166.5, 142.2, 133.6, 52.1, 38.9, 24.5. Calc. for $\text{C}_{12}\text{H}_{14}\text{O}_4$: C, 64.85; H, 6.35%. Found: C, 64.71; H, 6.28.

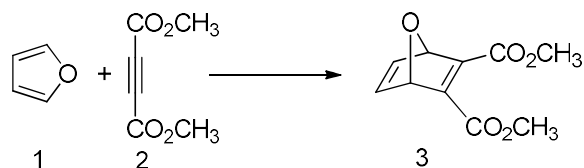
(1*R*,4*S*,5*S*,8*R*,8*aR*)-dimethyl 1,4,4*a*,5,8,8*a*-hexahydro-1,4-epoxy-5,8-ethanonaphthalene-2,3-dicarboxylate (**6**): Colorless oil. FTIR (cm^{-1}): ν = 2936, 2866, 1716, 1633, 1434, 1327, 1265, 1243, 1217, 1094, 923. ^1H NMR (400 MHz, CDCl_3): δ = 6.15 (dd, J = 4.8, 3.2, 2H), 4.91 (s, 2H), 3.81 (s, 6H), 2.80 (m, 2H), 2.01 (s, 2H), 1.53 (AA' part of AA'BB' system, quasi d, J = 18.0 Hz, 2H), 1.24 (BB' part of AA'BB' system, quasi d, J = 18.0 Hz, 2H), ^{13}C NMR (100 MHz, CDCl_3): δ = 163.2, 144.5, 131.9, 84.3, 52.2, 43.9, 32.9, 25.1, MS m/z : 290 (M^+), 259, 258 (M^+ , - OCH_3), 229, 230 (M^+ , - $\text{C}=\text{O}$), 199, 198, 197 (M^+ , - OCH_3), 185, 184 (M^+ , -O), 154, 153, 152 (M^+ , - $\text{C}=\text{O}$). Calc. for: $\text{C}_{16}\text{H}_{18}\text{O}_5$: C, 66.19; H, 6.25%. Found: C, 66.10; H, 6.19

2.4. Procedure for the Cycloaddition Reaction at High Pressure and in Hot Water²¹

Diene **3** (0.5 g, 2.4 mmol) and 1,3-cyclohexadiene (**4**) (0.197 g, 2.4 mmol) were dissolved in 20 mL of water in a stainless steel pressure reactor, and then the reaction was stirred at 40 bar N_2 and different temperature (25 and 50 °C) for 20 days. After the completion of the reaction it was extracted with EtOAc (3×10 mL) and dried over MgSO_4 . The solvent was evaporated on a rotary evaporator under reduced pressure. Then the product was chromatographed over silica gel using ethyl acetate:hexane (1:3) as the eluent to separate the product. At the end of the purification *retro* Diels-Alder product **5** and addition product **6** were obtained.

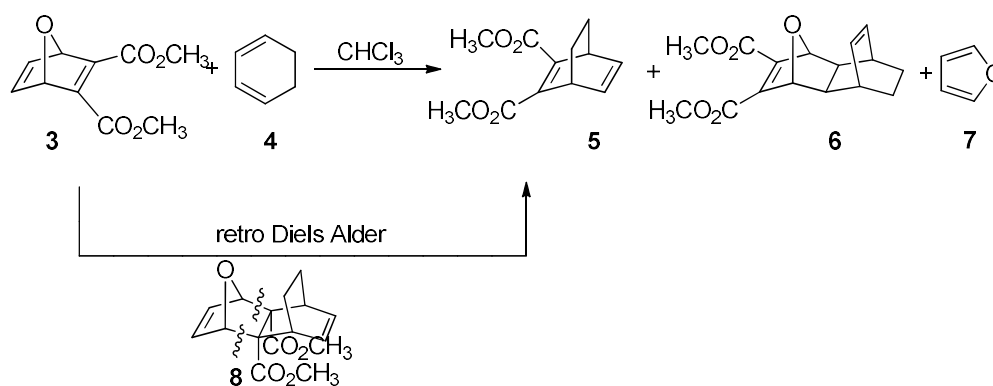
3. Results and Discussion

At the beginning, furan (**1**) and dimethyl acetylene dicarboxylate (**2**) were reacted, and produced dimethyl 7-oxa-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**3**)^{17,18} in high yield (Scheme 1).



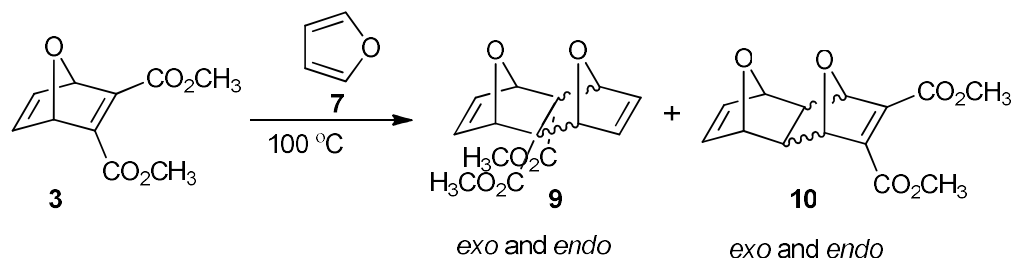
Scheme 1. The synthesis of dienophile **3**.^{17,18}

After the synthesis of dienophiles **3** (1.0 eq.) dienophile **3** was reacted with 1,3-cyclohexadiene (**4**) (1.0 eq.) in CHCl_3 without a catalyst at room temperature for 20 days; it was observed that very little product, *retro* Diels-Alder addition product **5** (5%) and Diels-Alder addition product **6** (9%), formed.

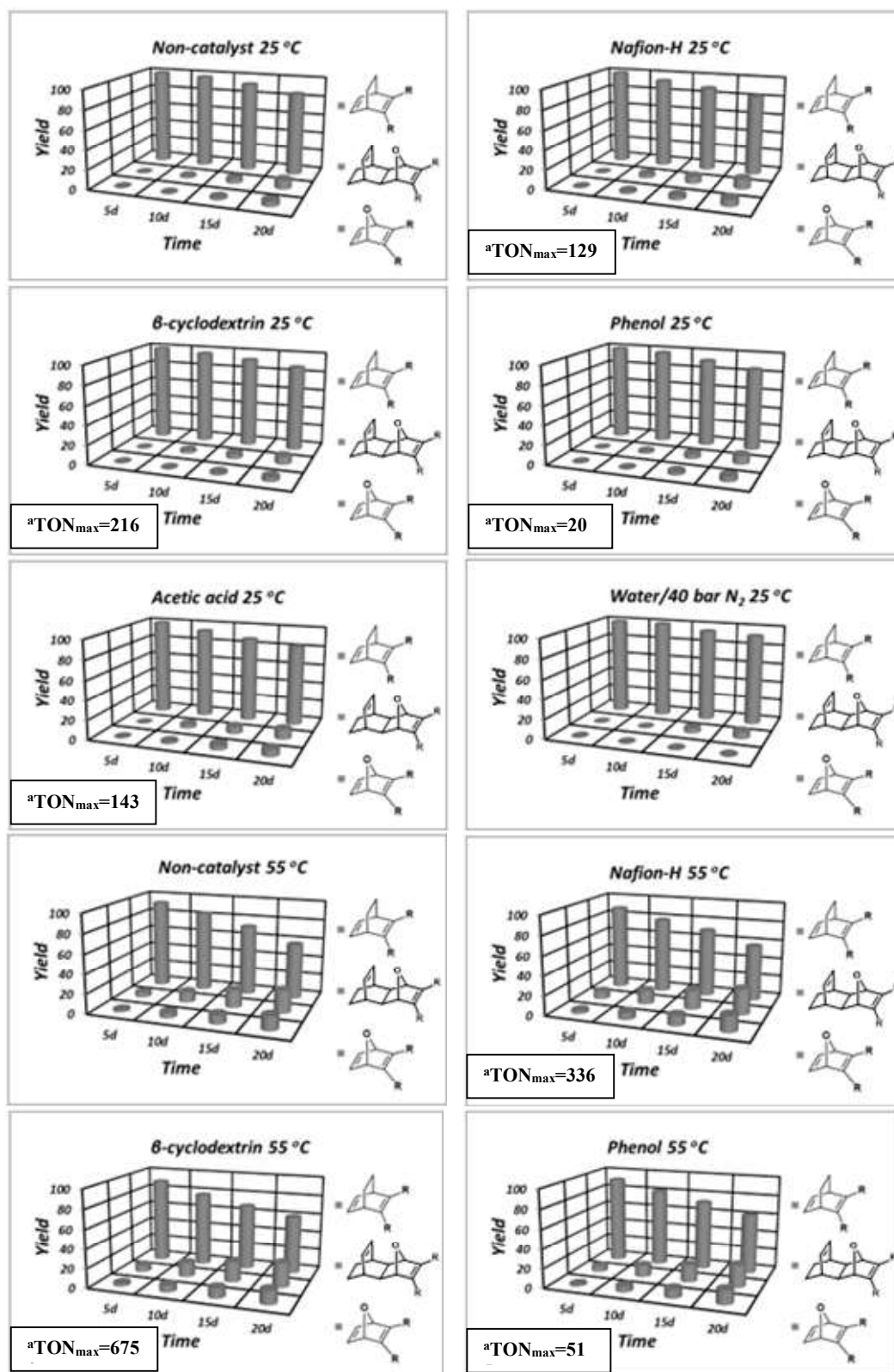


Scheme 2. Diels-Alder reaction of dienophile **3** with diene **4**.

Intermediate product (addition product over electron-deficient double bond) **8** is thermally unstable and breakage of the C-C bond results in *retro* Diels-Alder addition product **5** (Scheme 2). Thus, there are addition at both electron-deficient double bond and electron-rich double bond. There are similar examples in the literature. McCulloch et al.²² examined influence of Lewis acids on the Diels-Alder reaction and synthesized addition products over both electron-deficient double bond and electron-rich double bond at 100 °C.



Scheme 3. Diels-Alder reaction of dienophile **3** with diene **7**.²²



^aTurnover number (TON) = [(moles of limiting reactant (dienophile 3)) / moles of catalyst] × yield (20d)

Figure 1. Diels-Alder reaction of dienophile 3 and diene 4

To increase the yield, we decided to use different catalysts in this reaction (Table 1). Phenol, acetic acid, nafion and β -cyclodextrin, were used as the catalyst (Figure 1). Two products, **5**²⁰ and **6**, were obtained at the end of the reaction. Given the amount of product, it was observed that the catalyst alone was not effective. The results were similar to those of the reaction at room temperature. We decided to increase the reaction temperature. Increasing the temperature and using the catalyst increased the yield of the reaction very little, but that was not enough for us. Finally, when the reaction was performed at high pressure and in hot water, we saw that the yield of Diels-Alder addition product **6** was 61% (Figure 1). When we brought the conditions to high pressure and in hot water (40 Bar, 120 °C), we saw that the molecule has completely disintegrated.

There are 4 signals, three singlets (-CH=, -CH, and -OCH₃) and one AB system (-CH₂CH₂) as a quasi doublet ($J= 6.8$ Hz) in the ¹H NMR spectra of *retro* Diels-Alder addition product **5**. The ¹H NMR spectra of Diels-Alder addition product **6** have four signals. However, the exact structure of Diels-Alder addition product **6** was found by the COSY and NOESY NMR result. Diels-Alder addition product **6** shows that the oxygen and the double bond are on the same side. The double bond proton does not interact with bridge protons, because it is not in the same space.

Table 1. Diels-Alder reaction of dienophile **3** and diene **4** in various conditions

Reaction Conditions	Product	Yield%							
		25 °C				55 °C			
		5d	10d	15d	20d	5d	10d	15d	20d
No catalyst	3	100	98	93	86	93	84	73	63
	5	--	--	2	5	2	5	9	14
	6	--	2	5	9	5	11	18	23
Nafion-H	3	100	94	89	83	89	79	71	58
	5	--	2	4	7	3	7	10	16
	6	--	4	7	10	8	14	19	26
β -cyclodextrin	3	100	97	93	88	90	78	69	61
	5	--	--	2	4	3	7	10	14
	6	--	3	5	8	7	15	21	25
Phenol	3	100	98	92	86	92	82	73	63
	5	--	--	3	5	2	6	9	14
	6	--	2	5	9	6	12	18	23
Acetic acid	3	100	94	88	83	86	74	65	54
	5	--	2	5	7	5	9	13	17
	6	--	4	7	10	9	17	22	29
Water/40 bar N ₂	3	100	100	95	93	80	59	45	25
	5	--	--	--	--	3	7	10	14
	6	--	--	5	7	17	34	45	61

4. Conclusion

In summary, we achieved the chemoselective and *exo*-diastereo selective reaction between 1,3-cyclohexadiene and dimethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate without a catalyst, with small amounts of catalyst (nafion, β -cyclodextrin phenol and acetic acid), and in water (40 bar N₂, 55 °C). It was observed in the reaction that the effect of the catalyst was absent, the highest yield was at 40 bar atmosphere and 55 °C, it was the effect of the pressure (Table 1). The syntheses in water have potentially abundant applications, and it is hoped that this paper will motivate such efforts.

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Supporting Information

Supporting information accompanies this paper on <http://www.acgpubs.org/OC>

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