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Diels–Alder reactions: The effects of catalyst on the addition reaction

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ABSTRACT

The reaction between 2,3-dimethyl-1,3-butadiene and dimethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate is efficiently achieved with small amounts of catalyst, i.e. phenol, AcOH, nafion, and β–cyclodextrin. *Exo*-diastereoselective cycloaddition reactions were observed both without catalyst and different catalysts for 48 days. As a result, different products (tricyclicmolecule **5**, *retro*-Diels–Alder product **6**, and oxidation product **7**) were obtained with different catalysts. In addition, we synthesized Diels–Alders product **8** and tricyclocyclitol **10** via Diels–Alder reaction. The structures of these products were characterized by ^{1}H NMR, ^{13}C NMR, MS and IR spectroscopy.

1. Introduction

The cycloaddition of alkenes and dienes known as the Diels–Alder reaction is a very useful method for forming substituted cyclohexenes [1–9]. The reactions are normally synchronous and processes are concerted. The cycloaddition products are traditionally affected by modest solvents and catalysts, in accordance with small changes in charge on going from reactants to the activated complex [7,10].

The aim of our study was to obtain the cycloaddition products of dienophile **3** with 2,3-dimethyl-1,3-butadiene (**4**) using different catalysts (phenol, acetic acid, nafion, and β–cyclodextrin) at room temperature, and also without catalyst at 25 and 40 °C, in addition to synthesizing the cyclitol and epoxide derivatives (**9**, **10**).

2. Experimental

2.1. 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 (**6**) were prepared as described in the literature [11].

2.2. Diels–Alder reaction of dimethyl 7-oxo-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (3) with 2,3-dimethyl-1,3-butadiene

Diene **3** (0.5 g, 2.4 mmol) and 2,3-dimethyl-1,3-butadiene **4** (0.197 g, 2.4 mmol) was dissolved in 10 mL of chloroform, and then the reaction was stirred at room temperature for 48 days. After the reaction, the solvent was removed to give product.

(1R,4S,4aS,8aR)-dimethyl 6,7-dimethyl-1,4,4a,5,8,8a-hexahydro-1,4-epoxynaphthalene-4a,8a-dicarboxylate (***5***): M. P.: 85–87 °C ($CHCl_3$), **δ_H (400 MHz, $CDCl_3$):** 6.52 (s, 2H), 4.65 (2H, s), 3.56 (6H, s), 2.48 A part of AB system (2H, d, $J = 14.0$ Hz), 2.41 B part of AB system (2H, d, $J = 14.0$ Hz), 1.73 (6H, s, $-CH_3$) **δ_C (100 MHz, $CDCl_3$,)** 173.9, 135.4, 126.9, 86.8, 63.2, 51.8, 40.2, 18.8, **Anal. Calc.** for $C_{16}H_{20}O_5$: C 65.74, H 6.9. Found: C 65.66H 6.32%, **MS *m/z***: 209 (M^+, $-CH_3$), 194, 193, 192, 191 (M^+,CH_3), 179, 178, 177 (M^+, $-CH_3$), 166, 165, 164, 163 (M^+, −O), 134, 133, 132 (M^+, −C), 122, 121, 120 (M^+,-O), 107, 106, 105, 104, 103 (M^+,-C), **IR (cm^{-1})** = 1716.7 (−C=O).

Dimethyl 4,5-dimethylcyclohexa-1,4-diene-1,2-dicarboxylate (***6***) [12]: **M. P:** 72–72.6 °C ($CHCl_3$), (Lit.63–66 °C), **δ_H (400 MHz, $CDCl_3$):** 3.78 (s, 6H), 2.92 (s, 4H), 1.66 (s, 6H), **δ_C (100 MHz, $CDCl_3$):** 168.4, 132.7, 121.5, 52.1, 34.1, 17.9.

Dimethyl 4,5-dimethylphthalate (***7***) [12]: **M. P.:** 46–48 °C ($CHCl_3$) (Lit 56–57 °C) **δ_H (400 MHz, $CDCl_3$):** 7.42 (2H, s), 3.81 (6H, s), 2.24 (6H, s), **δ_C (100 MHz, $CDCl_3$):** 168.3, 140.2, 130.1, 129.4, 52.5, 19.7.

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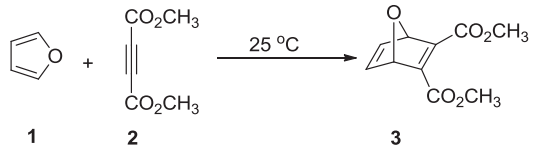
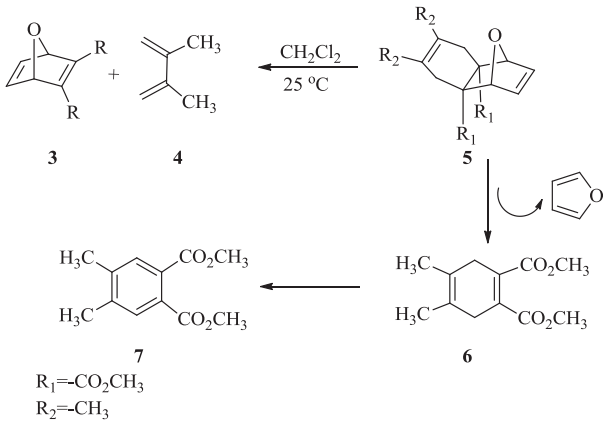


Scheme 1. Addition reaction of furan (**1**) and dimethyl acetylene dicarboxylate (**2**).



Scheme 2. Diels–Alder reaction of dienophile **3** and diene **4**.

2.3. Synthesis of (1aR,2R,2aS,7S,7aS)-dimethyl 4,5-dimethyl-1a,2,2a,3,6,6a,7,7a-octahydro-2,7-epoxynaphtho[2,3-b]oxirene-2a,6a-bis(carboperoxoate (*8*)

Diene **4** (0.500 g, 6.09 mmol) and epoxide **11** (1.38 g, 6.09 mmol) was dissolved in 10 mL of chloroform, and then the reaction was stirred at room temperature for 24 days. After the reaction, the solvent was removed to give 0.650 mg 95% yield of product **8**.

M. P.: 144–145 °C ($CHCl_3$), **δ_H (400 MHz, $CDCl_3$):** 4.23 (2H, s), 3.78 (2H, s), 3.61 (6H, s), 2.43 (2H, A part of AB system d, $J = 13.6$ Hz), 2.28 (2H, B part of AB system d, $J = 13.6$ Hz), 1.71 (6H, s), **δ_C (100 MHz, $CDCl_3$):** 172.7, 126.3, 82.8, 63.7, 52.1, 49.7, 39.3, 18.8, **Anal. Calc.** for $C_{16}H_{20}O_6$: C 62.33, H 6.54. Found: C 62.27, H 6.14%, **MS *m/z***: 308 (M^+, −2 O), 276 (M^+, $-CH_3$), 261, 262, 263 (M^+,-CO), 221, 220, 219, 218, 217 (M^+, $-CH_3$), 204, 203, 202, 201 (M^+, −CO), 177, 176, 174, 173 (M^+, $-2CH_3$) 147, 146, 145, 144, **IR (cm^{-1}):** 1716.3 (−C=O).

2.4. Synthesis of dimethyl 3,4-dimethyl-7-oxabicyclo[4.1.0]hept-3-ene-1,6-bis(carboperoxoate) (*9*)

Compound **5** (1.0 g, 3.42 mmol) was dissolved in 150 mL of chloroform, MCPBA (1.18 g, 6.84 mmol, 70%) was added, and then the reaction was stirred at reflux temperature for 3 days. The reaction mixture was added to 15 mL 50% $NaHSO_3$ solution and mixture was stirred for 15 min. The organic layer was separated and then washed with saturated aqueous $NaHCO_3$ (100 mL), dried with $MgSO_4$ and concentrated to give 740 mg of 90% yield of epoxide **9**.

M.P.: 64–65 °C ($CHCl_3$), **δ_H (400 MHz, $CDCl_3$):** 3.75 (6H, s), 2.86 (2H, d, $J_{2a,b} = J_{5a,b} = 19.6$ Hz), 2.64 (2H, d), 1,41 (s, 6H), **δ_C (100 MHz, $CDCl_3$):** 167.9, 131.3, 60.1, 52.3, 33.3, 19.1, **Anal. Calc.** for $C_{12}H_{16}O_5$: C 59.99, H 6.71, Found C 60.06, H 6.62%, **MS *m/z***: 240, (M^+, $-OCH_3$), 211, 210, 209, 208, 207, (M^+, −O), 194, 193, 192, 191, 190, (M^+, $-CH_3$), 179, 178, 177, 176, 175 (M^+,-CO), 151, 150, 149, 148, 147, (M^+, −CO), 123, 122, 121, 120, 119, (M^+, −O), 107, 106, 105, 104, 103, (M^+, −CO), **IR (cm^{-1}):** 1716 (−C=O).

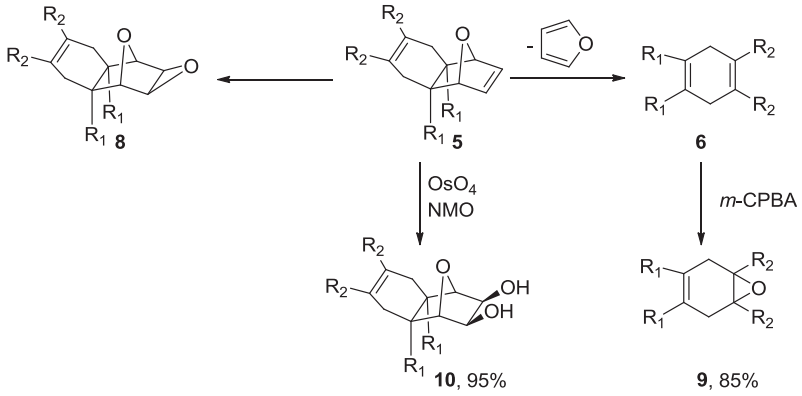
2.5. Synthesis of (1R,2S,3R,4S,8aS)-dimethyl 2,3-dihydroxy-6,7-dimethyl-1,2,3,4,4a,5,8,8a-octahydro-1,4-epoxynaphthalene-4a,8a-dicarboxylate (*10*)

To a stirred solution of tricyclic molecule **5** (1,0 g, 3.42 mmol) in 10 mL of acetone/H_2O (1:1) were added NMO (0.409 g, 3.42 mmol) and 2 ml of OsO_4 ($7{,}87.10^{-3}$ mmol) at room temperature. The mixture was stirred vigorously at room temperature for 24 h. The reaction was stopped. Evaporation of solvent gave 1.06 g of *cis*-diol **10** with 95% yield.

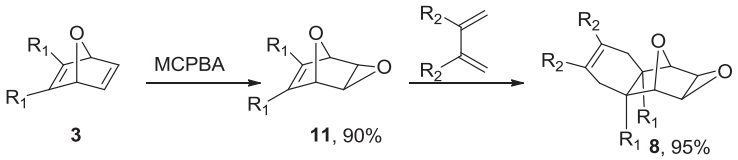
M. P.: 170–171 °C ($CHCl_3$), **δ_H (400 MHz, $CDCl_3$):** 4.56 (2H, s) 4.12 (2H, s), 3.62 (6H, s, $-OCH_3$), 3.22 (2H, bs, 2–OH), 2.42 (2H, d,

Table 1
Diels–Alder reaction of dienophile **3** and diene **4** (Scheme 2).

		% yield									
Catalyst	**Product**	3 h	6 h	12 h	24 h	30 h	48 h	6. d	15. d	30. d	48. d
Non-catalyst 25 °C	**3**	65	45	30	10	0	0	0	0	0	0
	5	35	55	70	90	98	95	75	62	20	5
	6 [12]	0	0	0	0	2	5	25	33	68	80
	7 [12]	0	0	0	0	0	0	0	5	12	15
40 °C	**3**	35	25	10	0	0	0	0	0	0	0
	5	65	75	90	90	85	73	11	0	0	0
	6 [12]	0	0	0	10	15	27	84	89	47	8
	7 [12]	0	0	0	0	0	0	5	11	53	92
Acetic acid 25 °C	**3**	50	30	14	2	0	0	0	0	0	0
	5	50	70	86	98	90	80	55	20	0	0
	6 [12]	0	0	0	0	10	20	45	60	67	30
	7 [12]	0	0	0	0	0	0	0	20	33	70
***β*–cyclo dextrin 25 °C**	**3**	55	35	20	10	0	0	0	0	0	0
	5	45	65	80	90	95	90	60	30	0	0
	6 [12]	0	0	0	0	5	10	40	55	67	35
	7 [12]	0	0	0	0	0	0	0	15	33	65
Nafion-H 25 °C	**3**	60	40	27	8	0	0	0	0	0	0
	5	40	60	73	92	95	90	65	40	0	0
	6 [12]	0	0	0	0	5	10	35	50	70	43
	7 [12]	0	0	0	0	0	0	0	10	30	57
Phenol 25 °C	**3**	55	35	20	5	0	0	0	0	0	0
	5	45	65	80	95	95	85	60	30	0	0
	6 [12]	0	0	0	0	5	15	40	55	69	38
	7 [12]	0	0	0	0	0	0	0	15	31	62



Scheme 3. The reaction of tricyclic molecule **5** with MCPBA and OsO_4/NMO.



Scheme 4. Synthesis of Diels–Alders product **8** from dienophile **3.**

J = 13.6 Hz), 2.28 (2H, d, J = 13.6 Hz), 1.69 (6H, s, $-CH_3$), **δ_C (100 MHz, $CDCl_3$):** 172.8, 126.4, 91.5, 72.0, 60.1, 52,1, 39.3, 18.8, **Anal. Calc.** for $C_{16}H_{22}O_7$: C 59.89, H 5.79, Found C 59.22, H 5.33%, **MS *m/z***: 326, (M^+, −2 CH_3), 297, 296, 295, 294, 293, (M^+, −CO), 268, 267, 266, 265, (M^+, −OH), 250, 249, 248, 247, (M^+, −OH), 233, 232, 231, 230, 229, (M^+, −CO), 202, 201, 200, 199, 198, (M^+, $-CH_3$) 187, 186, 185, 184, 183, (M^+, $-CH_3$) 171, 170, 169, 168, 167, (M^+,-O) 155, 154, 153, 152, 151, **IR (cm^{-1}):** 3480.2, 3405.8 (−OH), 1725.6, 1697.4 (−C=O).

2.6. Synthesis of (1R, 2R, 4S, 5S)-dimethyl 3,8-dioxatricyclo [3.2.1.$0^{2,4}$]oct-6-ene-6,7-dicarboxylate (**11**) [13,14]

1.0 g (4.76 mmol) of bicyclicdiene **3** was dissolved in 150 mL of chloroform, 1.66 g of MCPBA (9.62 mmol, 70%) was added, and then the reaction was stirred at room temperature for 3 days. The reaction mixture was worked up as described in the general procedure to give 1.02 g of epoxide **11** (95%). **M.P.** 82–83 °C ($CHCl_3$), (Lit. not found), **δ_H (400 MHz, $CDCl_3$):** 5.05 (2H, s), 3.76 (6H, s) 3.70 (2H, s), **δ_C (100 MHz, $CDCl_3$):** 161.4, 146.9, 78.7, 54.3, 51.6, **Anal. Calc.** for $C_{10}H_{10}O_6$: C 53.10, H 4.46, Found: C 53.25, H 4.34%, **MS *m/z***: 226, (M^+, $-OCH_3$), 195, 194, (M^+, $-OCH_3$), 167, 166, 165, 162.9, (M^+, −C=O), 139, 137, 136, 135, 134 (M^+, −C=O), 109, 108, 107, 106 (M^+, −C, −O), 81, 80, 79, 78, 77 (M^+, −C, −O), 55, 53, 52, 51, 50, **IR (cm^{-1}):** 1720 (−C=O).

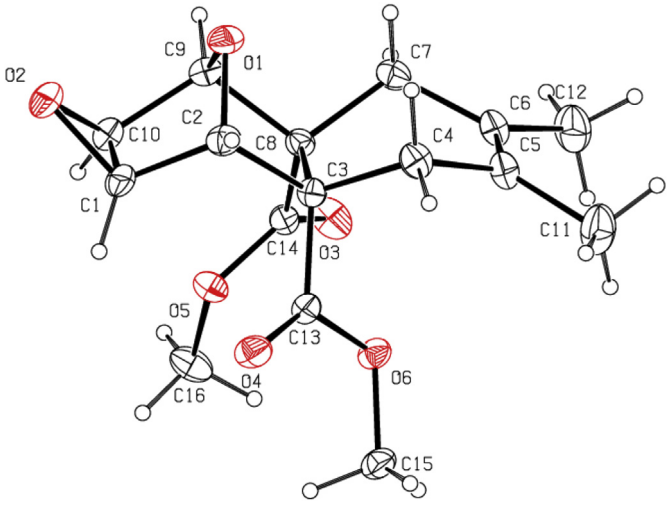


Fig. 1. ORTEP view of Diels–Alders product **8** showing the atom-labeling scheme. Displacement ellipsoids are drawn at the 40% probability level.

3. Results and discussion

In a preliminary study, dimethyl 7-oxa-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (**3**) [11] was prepared by the cycloaddition reaction of dimethyl acetylene dicarboxylate (**2**) to furan (**1**) in high yield (Scheme 1). Then, 1 M eq. dienophile **3** was reacted with 1 M eq. diene **4** in $CHCl_3$ without catalyst at room temperature (Scheme 2). After 24 h, the 90% conversion of tricyclic molecule **5** and 10% conversion of dienophile **3** were achieved according to ^{1}H NMR spectra of the mixture. ^{1}H NMR and ^{13}C NMR spectra of tricyclic molecule **5** were highly symmetrical due to the symmetry molecule. When the reaction was continued, after 30 h, *retro*-Diels–Alder product **6** [12] was observed with 2% conversion. The ^{1}H and ^{13}C NMR spectra were in good agreement with the structure of *retro*-Diels–Alder product **6**. *Retro*-Diels–Alder product **6** was synthesized by cycloaddition reaction of dimethyl acetylene dicarboxylate (**2**) to diene **4** in the literature [12]. After 6 days, 62% conversion of tricyclic molecule **5** and 33% conversion of *retro*-Diels–Alder product **6** were observed in ^{1}H NMR spectra of the mixture. When the reaction was continued, after 48 days, it was observed that the reaction was completed and 80% conversion of *retro*-Diels–Alder product **6** [12], 15% conversion of oxidation product **7** [12] and 5% conversion of tricyclic molecule **5** were achieved. The structural assignments of the oxidation product **7** are based on their spectroscopic data. When the reaction temperature was 40 °C, it was observed that the reaction speed was in parallel with an increase in the amount of *retro*-Diels–Alder product **6** and oxidation product **7** (Table 1).

In a secondary study, 1 M eq. dienophile **3** and 1 M eq. diene **4** were dissolved in $CHCl_3$ with acetic acid at 25 °C and it was observed that dienophile **3** ran out after 30 h. At the end of the reaction, 30% of *retro*-Diels–Alder product **6** remained in the reaction medium with 70% converted to oxidation product **7** under acetic acid catalyzed conditions; this is higher than conversion achieved by the reaction in which no catalyst was used. In contrast, 70% conversion of oxidation product **7** was achieved in the reaction. When we used β–cyclodextrin and phenol as catalyst, similar outcomes were observed. When phenol was used as catalyst, about 60% conversion of oxidation product **7** and 40% conversion *retro*-Diels–Alder product **6** were seen. The reaction with nafion as catalyst gave 57% conversion of oxidation product **7** and 43% conversion of *retro*-Diels–Alder product **6** after 48 days. Finally, in terms of reaction yield of tricyclic molecule **5** with acetic acid as catalyst, *retro*-Diels–Alder product **6** and oxidation product **7** at 40 °C were synthesized in high yield (Table 1).

After the successful isolation and characterization of all molecules, we turned our attention to the fragmentation of tricyclic molecule **5**. First, we tried the oxidation reaction of tricyclic molecule **5** with *m*-CPBA. At the end of the reaction, tricyclic molecule **5** was fragmented into diene **6** and diene **6** gave the epoxidation reaction. At the end of the epoxidation reaction, epoxide **9** was obtained in 85% yield. Although the reaction of tricyclic molecule **5** with OsO_4/NMO (N-methyl morpholine N-oxide) gave tricyclic molecule **10** in 95% yield, degradation was not observed in this reaction (Scheme 3).

Next, dienophile **3** was converted to the desired epoxide **11** [13,14] in the presence of MCPBA in CH_2Cl_2 at 25 °C in 90% yields. When the epoxide **11** was reacted with 2,3-dimethy-1,3-butadiene (**4**) in $CHCl_3$, the desired Diels–Alders product **8** was obtained in good yield (Scheme 4). In addition, the exact structure of Diels–Alders product **8** was determined by X-ray diffraction analysis (Fig. 1).

3.1. Crystallography

Single crystals of Diels–Alders product **8** were obtained by slow evaporation of the compounds in acetonitrile at room temperature. Selected single-crystal of Diels–Alders product **8** was used for data collection on a Bruker SMART BREEZE CCD diffractometer. The graphite-monochromatized MoK_α radiation (λ = 0.71073 Å) and oscillation scans technique with $\Delta\omega = 5°$ for one image were used for data collection. The lattice parameters were determined by the least-squares methods on the basis of all reflections with $F^2 > 2\sigma(F^2)$. Integration of the intensities, correction for Lorentz and polarization effects and cell refinement was performed using Bruker SAINT (Bruker AXS Inc, 2012) software [15]. The structures were solved by direct methods using SHELXS-97 [16] and refined by a full-matrix least-squares procedure using the program SHELXL-97 [16]. H atoms were positioned geometrically and refined using a riding model. The final difference Fourier maps showed no peaks of chemical significance. *Crystal data* for **8**: $C_{16}H_{20}O_6$, crystal system, space group: triclinic, P-1; (no:2); unit cell dimensions: a = 7.0375(5), b = 8.2899(5), c = 13.6981(9) Å, α = 93.342(4), β = 101.770(5), γ = 101.610(4) Å; volume: 762.22(9) Å^3; Z = 2; calculated density: 1.343 g/cm^3; absorption coefficient: 0.103 mm^{-1}; F(000): 328; θ-range for data collection 1.5–26.4°; refinement method: full matrix least-square on F^2; data/parameters: 2439/201; goodness-of-fit on F^2: 1.183; final R-indices [$I > 2\sigma(I)$]: $R_1 = 0.116$, w$R_2 = 0.215$; largest diff. peak and hole: 0.863 and −0.387 e Å^{-3}.

4. Conclusion

In summary, we achieved the *chemo*selective and *exo*-diastereoselective reaction between 2,3-dimethyl-1,3-butadiene and dimethyl 7-oxabicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate without catalyst and with small amounts of catalyst (phenol, acetic acid, nafion, and β-cyclodextrin). In addition, we described a useful method for the synthesis of important tricylocyclitol and dioxatricyclo derivatives useful molecules with anticancer, antibiotic, anti-feedant, and anti-leukemic activity and versatility as synthetic intermediates.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.molstruc.2015.06.012.

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