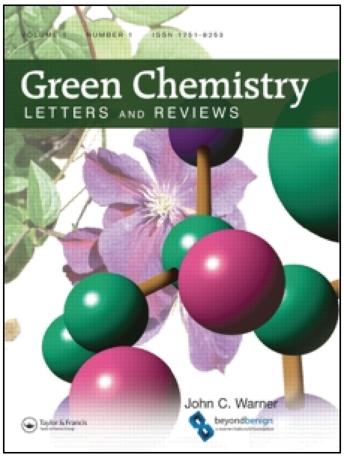


Green Chemistry Letters and Reviews
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t748292817

Diels-Alder reactions in the presence of a minimal amount of water

Nicole Windmon[a]; Veljko Dragojlovic[b]
[a] Department of Chemistry, Florida Atlantic University, Boca Raton, FL, USA [b] Wilkes Honors College of Florida Atlantic University, Jupiter, FL, USA

To cite this Article Windmon, Nicole and Dragojlovic, Veljko(2008) 'Diels-Alder reactions in the presence of a minimal amount of water', Green Chemistry Letters and Reviews, 1: 3, 155 — 163
To link to this Article: DOI: 10.1080/17518250802482505
URL: http://dx.doi.org/10.1080/17518250802482505

Green Chemistry Letters and Reviews
Vol. 1, No. 3, September 2008, 155–163

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Diels-Alder reactions in the presence of a minimal amount of water

Nicole Windmon[a] and Veljko Dragojlovic[b]*

[a]*Department of Chemistry, Florida Atlantic University, Boca Raton, FL, USA;* [b]*Wilkes Honors College of Florida Atlantic University, Jupiter, FL, USA*

(Received 21 August 2008; final form 16 September 2008)

Diels-Alder reactions of neat reactive dienes and dienophiles are frequently vigorous and have a limited preparative value. It is possible to control the temperature of multi-gram scale Diels-Alder reactions by adding a minimal amount of water to neat reactants. In addition, the presence of water resulted in an increased reaction rate and formation of a higher purity product. The use of minimal amounts of other solvents, with lower heat capacities, did not give good results. Furthermore, some dienophiles, e.g. maleic anhydride, reacted poorly in a dilute water suspension or solution, but worked well in the presence of a minimal amount of water. This is an environmentally friendly, practical and efficient approach to preparation of Diels-Alder adducts on a multi-gram scale.

Keywords: Diels-Alder; solvent-free; on-water; cyclopentadiene

Introduction

In recent years, a great deal of effort has been focused on replacing toxic and hazardous organic solvents by carrying out organic reactions in water or without a solvent. So far, only a few Diels-Alder reactions under solvent-free conditions (SFC) have been reported (*1–3*). Diels-Alder reactions have been done in water as a solvent, or a co-solvent for some time (*4–11*). A recent improvement has been an introduction of "on water" reactions (*12*). The focus of most of the work has been on the acceleration of slow Diels-Alder reactions and water has been used to increase the reaction rate of less reactive systems. Rate acceleration of Diels-Alder reactions by water had been attributed to hydrophobic effects (*6,13–15*), enhanced hydrogen bonding in the transition state (*7,13–15*), cohesive energy density (*11*), ground state destabilization, micellar catalysis (*8,16*), or interfacial hydrogen bonding (*10*). Breslow and Grieco's groups reported rate acceleration of Diels-Alder reactions in either suspension or homogeneous aqueous solutions, when compared with the SFC reactions or organic solvent-based reactions (*5,16–18*). On the other hand, vigorous Diels-Alder reactions have received little attention. For example, a recent study showed that solvent-free dimerization of cyclopentadiene on a one mole scale is explosive under adiabatic conditions (*19*). While such reactions can always be slowed down by diluting the reaction mixture with a solvent, it would be beneficial to run them under solvent-free or as close to SFC as possible. Such procedures would be both more environmentally friendly and would simplify isolation of the products. We wish to report a variation of the "on water" reaction procedure in which neat reactants are mixed in the presence of only a minimal amount of water.

Results and discussion

In this study, reactions were done in the smallest possible flasks in order to minimize heat loss and emphasize the effect of water. The shape and size of the reaction vessel was important. The use of larger flasks, in which the reaction mixture has lower depth and greater contact with the flask walls and air, allows a more efficient heat dissipation and should be considered when scaling up reactions.

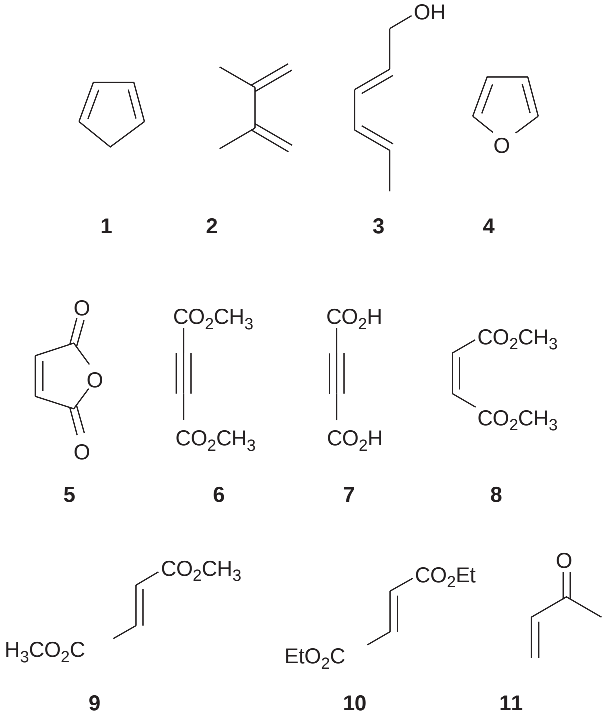
Common dienes **1**–**4** and dienophiles **5**–**11** have been investigated (Scheme 1). In a number of cases, particularly with cyclopentadiene, the reaction was very vigorous and the reactants boiled out of the flask. The addition of a small amount of water helped to maintain the reaction temperature under control. It appears that the principal role of water was to absorb the heat evolved in the course of a reaction. The addition of the same amount of a solvent with a lower heat capacity such as methanol, ethanol, or acetone gave inferior results (Figure 1). Further

---

*Corresponding author. Email: vdragojl@fau.edu

ISSN 1751-8253 print/ISSN 1751-7192 online

DOI: 10.1080/17518250802482505
http://www.informaworld.com



Scheme 1.

evidence to that effect is that when water is added in the form of ice a smaller amount was needed (Figure 2). Thus, one can reduce the amount of water needed, by using crushed ice instead. In some cases, the addition of a small amount of water resulted not only in lower reaction temperature but also in an increased reaction rate and the formation of a higher purity product.

Although in most cases, at least one of the reactants was a solid (Table 1, entries 1, 3, 5, 8, 9 and 10) and the reaction mixture was initially heterogeneous, the reactions themselves occurred in a liquid phase through formation of a homogeneous melt before the product solidified (*20*). With one exception (Table 1, entry 1), attempts to use an ice bath to control the reaction temperature failed as a low reaction temperature prevented formation of a melt and the starting materials were recovered. In most cases, there was an induction time of at least several minutes followed by an exothermic reaction. Some, but not all, of the reactions required an induction time for the formation of a melt. Besides absorbing the heat, the addition of a small amount of water appeared to speed up formation of a melt. Frequently, once the reaction mixture liquefied, two distinct liquid layers appeared, which mixed, in a highly exothermic process, to give a homogeneous clear liquid. In the case of solid reaction products, solidification of the reaction mixture followed, which was a slightly exothermic process. An exception to this general behavior was the reaction of cyclopentadiene **1** and maleic anhydride **5**, which was instantaneous and vigorous.

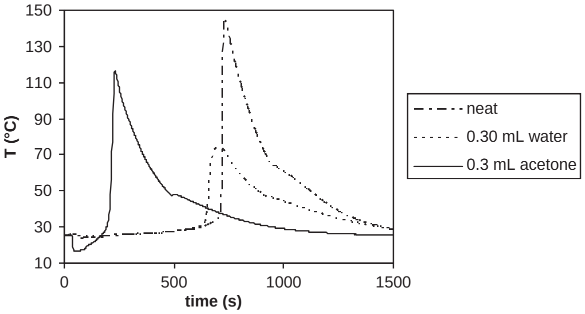


Figure 1. Temperature change in a reaction of 2,3-dimethyl-1,3-butadiene **2** with maleic anhydride **5** on 10 mmol scale.

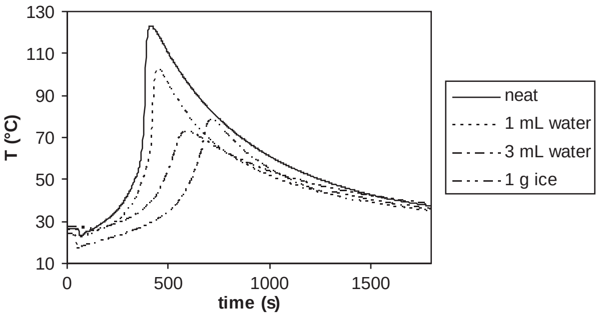


Figure 2. Reaction of cyclopentadiene **1** and dimethyl fumarate **9** on 0.10 mol scale.

The reaction of cyclopentadiene and maleic anhydride (Table 1, entry 1) without a solvent has been reported to be explosive (*21*). Indeed, in our hands it was a highly exothermic reaction. The addition of even a small amount of cyclopentadiene to powdered maleic anhydride resulted in a very vigorous reaction. The residue turned into a hard solid, which was unreactive toward additional cyclopentadiene. The solid was composed of various amounts of maleic anhydride and a mixture of *exo*- and *endo*-isomers in various ratios (~3–5% of *exo*-isomer). On a 0.01 mole scale, even in the presence of 0.7 mL of water, the reaction temperature exceeded 42°C (boiling point of cyclopentadiene). Furthermore, the major product was a result of hydrolysis (28% of the anhydride **12** and 57% of the corresponding diacid were isolated). Unlike other reactions in this study, which exhibited some induction time, the reaction between cyclopentadiene and maleic anhydride was instantaneous and did not appear to involve the formation of a melt. In this case, the use of an ice bath along with a smaller amount of water (0.4 mL) was sufficient to keep the reaction temperature under control while, at the same time, preserving the

Table 1. Diels-Alder reactions under solvent-free conditions and in the presence of a minimal amount of water.

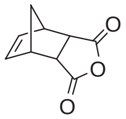
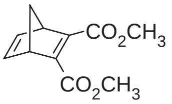
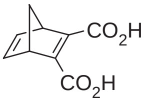
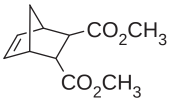
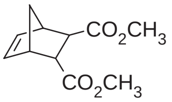
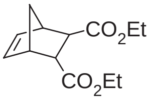
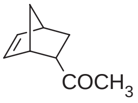
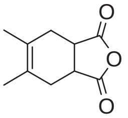
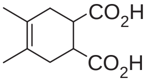
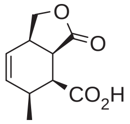
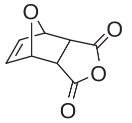
Entry	Diene	Dienophile	Product(s)	Yield (%), (Ratio *endo*:*exo*)	
				SFC	Water
1	**1**	**5**	 **12**	–	74[a] (98:2)[b]
2	**1**	**6**	 **13**	–	89[c]
3	**1**	**7**	 **14**	–	88[c]
4	**1**	**8**	 **15**	90[c] (3.2:1)[b]	87[c] (3.4:1)[b]
5	**1**	**9**	 **16**	87[c]	85[c]
6	**1**	**10**	 **17**	–	95[c]
7	**1**	**11**	 **18**	88[c] (4:1)[b]	84[c] (4.8:1)[b]
8	**2**	**5**	 **19**  **20**	93[c]	67[a] (**19**) 8[a] (**20**)

Table 1. (*Continued*)

Entry	Diene	Dienophile	Product(s)	Yield (%), (Ratio *endo*:*exo*)	
				SFC	Water
9	**3**	**5**	 **21**	–	96[c] (100:0)[d]
10	**4**	**5**	 **22**	68[a] (0:100)[d]	75[a] (0:100)[d]

[a]Yields of pure products after either chromatography or recrystallization; [b]Determined by GC; [c]Yields of crude products, which were >95% pure by GC; [d]Determined by ^{1}H NMR.

anhydride functionality. Anhydride **12** was isolated in 74% yield. When an ice bath alone was used, it was more difficult to control reaction temperature.

The solvent-free reaction of cyclopentadiene **1** with dimethyl acetylenedicarboxylate **6** (Table 1, entry 2) was vigorous and cyclopentadiene (1.5 equivalents) had to be added over a period of time to keep the reaction mixture from boiling over. The reaction temperature was considerably lower when water was added, which made it simpler to run the reaction as there was no need to use a condenser, no need for a slow addition, and reactants could be used in equimolar amounts. In either case the reaction product was pure. In general, when the reaction was scaled up, the amount of water needed to keep the reaction temperature under control sharply increased. A reaction of cyclopentadiene with dimethyl acetylenedicarboxylate was a good example. On a 10 mmol scale only 0.10 mL of water was required while doubling the reaction scale to 20 mmol increased the necessary amount of water to 4 mL (Figure 3).

The reaction between cyclopentadiene **1** and acetylenedicarboxylic acid **7** (Table 1, entry 3) was unique, in that it did not proceed at all under SFC and a violent reaction ensued upon the addition of only a small amount (a single drop) of water. While the reaction on a 10 mmol scale can be successfully done in the presence of 0.30–0.50 mL of water, the addition of 0.70 mL of water resulted in a consistently reproducible reaction and a yield of 88%. The reaction was completed within ~25 minutes, and the product solidified within another ~20 minutes. Water appeared to play several roles – it dissolved some of the starting diacid providing a reaction medium, it speeded up the formation of a melt and absorbed the heat of the reaction. This reaction worked very well under "on water" conditions (*12*) (1M concentration of the reactants) to give a pure diacid in 81% yield.

Reactions of somewhat less reactive dienophiles, such as dimethyl maleate **8**, dimethyl fumarate **9**, diethyl fumarate **10** and methyl vinyl ketone **11** (Table 1, entries 4–7), worked well under SFC and could be scaled up to ~ 0.1–0.3 mol before water had to be added to control the reaction temperature (Figure 4). There was only a minor, but reproducible, increase in preference for the formation of the *endo*-isomer when a minimal amount of water was added.

It has been established that the efficiency of mixing affects the reaction rate (*22*). A good example is a comparison of reaction rates of dimethyl fuma-

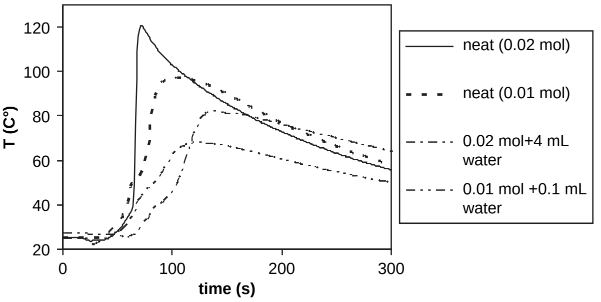


Figure 3. Reactions cyclopentadiene **1** and dimethyl acetylenedicarboxylate **6** on 10 mmol and 20 mmol scales.

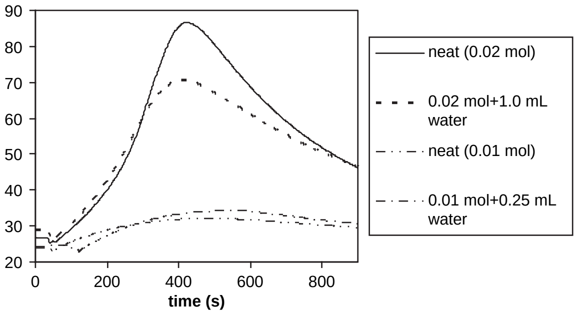


Figure 4. Reactions of cyclopentadiene **1** and methyl vinyl ketone **11** on 0.01 mol and 0.02 mol scales.

rate **9** (solid) and diethyl fumarate **10** (liquid) with cyclopentadiene **1** (Figure 5). As the efficiency of mixing of liquid reactants is obviously better, the reaction rate was correspondingly higher.

In a solvent-free reaction of 2,3-dimethyl-1,3-butadiene **2** with maleic anhydride **5** (Table 1, entry 8) a pure single product was obtained in a high yield. However, the reaction temperature went out of control (Figure 1) and an excess of 2,3-dimethyl-1,3-butadiene (two equivalents) had to be used. The addition of a small amount of acetone resulted in a very fast reaction that also went out of control. In the presence of a small amount of water the reaction temperature was more moderate. However, some hydrolysis of the anhydride was observed. An attempt to use an ice bath to control the reaction temperature failed – due to a low reaction temperature, there was no formation of a melt and most of the starting materials were recovered.

While most of the Diels-Alder reactions in this study involved at least one liquid component, the reaction between (2*E*,4*E*)-2,4-hexadien-1-ol **3** and maleic anhydride **5** (Table 1, entry 9) was a solid-solid reaction. The presence of water in both reduced the maximum reaction temperature as well as considerably reduced the reaction time. The reaction had already been reported to work well under SFC through formation of a melt (*23*). The stereochemistry of the product had been established as *cis* (*endo*-addition) (*24*). The reaction on up to 5 mmol scale can be successfully done as a solvent-free reaction. However, with an increase in reaction scale, heat becomes more difficult to dissipate and for good results, one has to add water. Furthermore, the addition of a small amount of water apparently speeded up the formation of a melt. No hydrolysis of the anhydride was observed, presumably because the intramolecular lactone formation is a more facile reaction. On a 10 mmol scale in a 50 mL beaker, the reaction on neat reagents was highly exothermic and gave a product that was only ~90% pure as determined by gas chromatography (GC). A SFC reaction on the same scale (10 mmol) with liquid (2*E*,4*E*)-2,4-hexadien-1-ol (mp 31°C) went out of control (reaction temperature in different runs was 160–210°C) and the resulting product was a complex mixture. This reaction did not work as an "on water" reaction (1M suspension of the reactants in water).

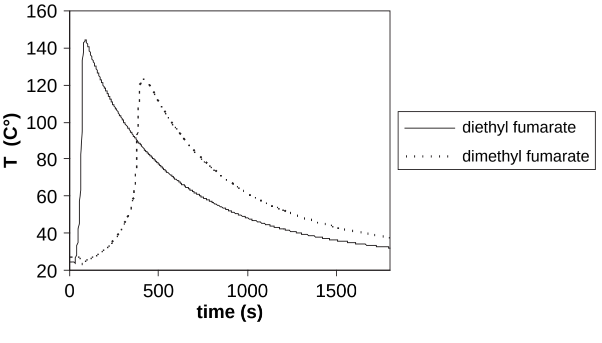


Figure 5. Reactions of cyclopentadiene with neat diethyl and dimethyl fumarates on 0.30 mol scale.

Compared to other dienes in this study, furan was the least reactive. It is interesting that the initial addition of furan **4** to maleic anhydride **5** (Table 1, entry 10) was a highly endothermic process. No hydrolysis of the anhydride was observed. The reaction product was allowed to dry in air and was rinsed with a small amount of dichloromethane to remove unreacted maleic anhydride. In each case, the product was pure (>95% by ^{1}H NMR; see Supplementary Material online for the proton NMR; spectra of the products) and was obtained in a good yield (~80%) even in solvent-free reactions in which reaction temperature exceeded 70°C. While dichloromethane rinse makes the process less environmentally friendly, it gave better results compared to a recrystallization from ethyl acetate-hexanes mixture (*25*), which resulted in some decomposition of the product and lower yields (*4*).

There appears to be an optimal point in each reaction where the addition of a small amount of water is the most beneficial. A reaction involving a number of substrates can be done on a small scale (5–10 mmol or less) as a solvent-free reaction. Thus, Diels-Alder reactions of cyclopentadiene (**1**) and some unsaturated esters, such as dimethyl maleate (**8**) and fumarate (**9**) as well as methyl vinyl ketone (**11**) on a <5 mmol scale do not generate much heat, are very slow (take days) and often do not go to completion. With an increase in the reaction scale there is a point where heat cannot dissipate as efficiently, as a consequence of the increased reaction temperature reactions become considerably faster, and usually go to completion in one hour or less. Thus, a reaction on a smaller scale should be done in as small a vessel as possible in order to retain the heat

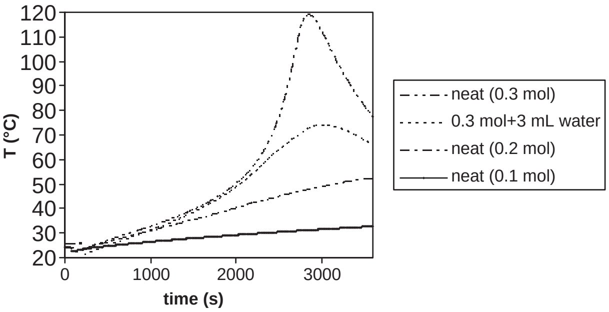


Figure 6. Reactions of cyclopentadiene **1** and dimethyl maleate **8** on 0.1, 0.2 and 0.3 mol scales. The reactions on 0.1 and 0.2 mol scales were monitored past 1 h shown in the graph and the reaction temperatures did not exceeded 36°C and 54°C, respectively.

and ensure that the reaction proceeds at a reasonable rate and goes to completion, while a reaction on a larger scale should be done in much larger vessels to allow dissipation of excess heat. The further increase in reaction scale results in an out of control runaway reaction. At this point, the addition of a minimal amount of water ensures that the reaction temperature is maintained under control. If the reaction is scaled up even further, the amount of water needed to keep the reaction under control sharply increases. We have been able to scale reaction up to 0.6 mol ($\sim$100 g of the dienophile–diethyl fumarate). The temperature change in the course of scaling up of the reaction of cyclopentadiene **1** with dimethyl maleate **8** is shown in Figure 6. Some systems, such as maleic anhydride and (2*E*,4*E*)-2,4-hexadien-1-ol worked well on small scale ($<$5 mmol), and on an intermediate scale (10–50 mmol) in the presence of water.

Finally, some reactions did not work very well when diluted with larger amount of water – which can be considered to represent more traditional "on water" conditions. For example, in our hands the reaction between methyl vinyl ketone and cyclopentadiene in a 1 M water suspension, gave only a modest yield of 2-acetoxy-5-norbornene **18** due to a competing dimerization of cyclopentadiene. In addition, most of the reactions in 1 M water suspension/solution involving maleic anhydride either failed or afforded products in low yields.

Conclusion

In summary, the addition of a minimal amount of water appears to be the most beneficial with highly exothermic Diels-Alder reaction systems on a moderate, multi-gram, scale. When further scaling up the reaction, one has to use progressively larger amounts of water. The main role of water appeared to be to absorb the heat of reaction. Other roles involve facilitating formation of a melt and, in some cases, at least partially dissolving the reactants providing a reaction medium. The developed procedure is advantageous when compared to the traditional "on water" in that it employs only a minimal amount of water thus simplifying the work up. Frequently, air-drying of the product was the only work up needed. Besides the addition of water, when scaling up a solvent-free Diels-Alder reaction one should consider the shape and size of the reaction vessel as well as the efficiency of mixing of the reactants. The main features of the process are that it maximizes the incorporation of the starting materials into the product, generates little or no waste, is done under ambient temperature and pressure, is solvent-free, utilizes neither reagents nor catalysts, reaction progress can be monitored in real time by monitoring the temperature and isolation of the products requires little or no work up. Thus, it conforms to most of the 12 green chemistry principles (*26*).

Experimental

General

Temperature measurements were recorded using a Vernier Stainless-Steel Temperature Probe connected to Texas Instruments TI 83 calculator by means of Vernier LabPro^{TM} interface. Data were transferred to a PC as an Excel file. Separations were done either by column chromatography or by preparative radial thin layer chromatography (Harrison Chromatotron). ^{1}H NMR spectra were recorded on a Bruker Avance 400 spectrometer in $CDCl_3$ solutions, except for the compounds **14** and **21**, which were recorded in acetone-D_6. Gas Chromatography–Mass Selective Detector (GC-MSD) analyses were performed by means of Agilent 6890N Gas Chromatograph equipped with HP-5MS 30 m × 0.25 mm column (Cat. No. 19091S-433) and Agilent 5973N MSD. Melting points were taken with MelTemp II apparatus and are uncorrected. Cyclopentadiene is obtained by cracking of dicyclopentadiene (*27*). Dicyclopentadiene, 2,3-dimethyl-1,3-butadiene, (2*E*,4*E*)-2,4-hexadien-1-ol, furan, maleic anhydride, acetylene dicarboxylic acid, dimethyl acetylenedicarboxylate, dimethyl maleate, dimethyl fumarate, diethyl fumarate and methyl vinyl ketone were purchased from Acros Organic and used without further purification. Acetone, hexanes, dichloromethane and ethyl acetate were purchased from Fisher Scientific Company and used without further purification. Deuterated solvents and silica gel were purchased from Aldrich Chemical Company and used without further purification. All of the isolated products were known compounds and gave satisfactory ^{1}H NMR and

GC-MS data. ^{1}H NMR spectra of all the isolated compounds (**12** (*28*), **13** (*29*), **14** (*30*), *exo*- and *endo*-**15** (*31*), **16** (*32*), **17** (*33*)**, 18** (*34*), **19** (*34*), **21** (*35*) and **22** (*36*)) have been reported in the literature.

Cis-*5-norbornene-2,3-dicarboxylic anhydride (12)*

A temperature probe, a stirring bar and 0.98 g (10 mmol) of maleic anhydride were placed in a 10 mL round bottom flask. The flask was cooled in an ice bath. The mixture was stirred vigorously and 0.40 mL of water was added followed by a slow addition (over a period of two minutes) of 0.91 mL (11 mmol) of cyclopentadiene. The product was recrystallized from ethyl acetate/hexanes to give 1.22 g (74%) of *cis*-5-norbornene-2,3-dicarboxylic anhydride (**12**); mp. 163–164°C (lit. 165°C (*37*)).

Dimethyl bicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylate (13)

A temperature probe, a stirring bar and dimethyl acetylenedicarboxylate (2.50 mL, 20 mmol) were placed in a 10 mL round bottom flask. Water was added (4.00 mL) followed by cyclopentadiene (1.67 mL, 20 mmol). Stirring was continued for 10 minutes. The product was dissolved in ethyl acetate (10 mL), dried (anh. $MgSO_4$) and ethyl acetate was removed by distillation under reduced pressure to give 3.70 g (89%) of dimethyl bicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylate (**13**).

Bicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylic acid (14)

A stirring bar and acetylene dicarboxylic acid **7** (1.14 g, 10 mmol) were placed in a 10 mL round bottom flask. Water was added (0.70 mL) followed by cyclopentadiene **1** (0.83 mL, 10 mmol). Stirring was continued for 25 minutes. The solid product was rinsed with a small amount of hexane and left to dry in air. Yield of bicyclo[2,2,1]hept-2,5-diene-2,3-dicarboxylic acid (**14**) was 1.58 g (88%); mp. 164°C (d) (lit. 158.2–159.2°C (*38*)).

Dimethyl cis-*5-norbornene-2,3-dicarboxylate (15)*

A temperature probe, a stirring bar and cyclopentadiene (24.9 mL, 0.30 mol) were placed in a 100 mL round bottom flask. Water was added (3.00 mL) followed by dimethyl maleate (37.5 mL, 0.30 mol). Stirring was continued for a total of 60 minutes. The product was dissolved in ethyl acetate (20 mL), dried (anh. $MgSO_4$) and ethyl acetate was removed by distillation under reduced pressure to give 54.6 g (87%) of a mixture of *endo*- (**15a**) and *exo*- (**15b**) isomers.

*Dimethyl 5-norbornene-2-*endo*,3-*exo*-dicarboxylate (16)*

A temperature probe, a stirring bar and dimethyl fumarate (14.41 g, 0.10 mol) were placed in a 100 mL round bottom flask. Ice was added (1.00 g) followed by cyclopentadiene (8.30 mL, 0.10 mol). Stirring was continued for a total of 30 minutes. The product was dissolved in ethyl acetate (30 mL), dried (anh. $MgSO_4$) and ethyl acetate was removed by distillation under reduced pressure to give 17.80 g (85%) of dimethyl 5-norbornene-2-*endo*,3-*exo*-dicarboxylate (**16**).

*Diethyl 5-norbornene-2-*endo*,3-*exo*-dicarboxylate (17)*

A temperature probe, a stirring bar and diethyl fumarate **10** (98.80 mL, 0.60 mol) were placed in a 500 mL round bottom flask. Ice was added (40 g) followed by cyclopentadiene **1** (49.80 mL, 0.60 mol). Stirring was continued for a total of 30 minutes. The product was separated from water. Water was extracted with ethyl acetate (3x5 mL) and the extracts were combined with the organic product. Ethyl acetate solution was dried (anh. $MgSO_4$) and ethyl acetate was removed by distillation under reduced pressure to give 136.19 g (95%) of diethyl 5-norbornene-2-*endo*,3-*exo*-dicarboxylate (**17**).

2-Acetyl-5-norbornene (18)

A temperature probe, a stirring bar and cyclopentadiene (1.67 mL, 20 mmol) were placed in a 10 mL round bottom flask. Water was added (0.25 mL) followed by methyl vinyl ketone (1.70 mL, 20 mmol). Stirring was continued for a total of 15 minutes. The product was dissolved in ethyl acetate (10 mL), dried (anh. $MgSO_4$) and ethyl acetate was removed by distillation under reduced pressure to give 2.28 g (84%) of a mixture of *endo*- and *exo*-2-acetyl-5-norbornene (**18**).

4,5-Dimethyl-4-cyclohexene-1,2-dicarboxylic anhydride (19) and 4,5-dimethyl-4-cyclohexene-1,2-dicarboxylic acid (20)

A temperature probe, a stirring bar and 0.98 g (10 mmol) of maleic anhydride were placed in a 10 mL round bottom flask. The mixture was stirred vigorously and 0.30 mL of water was added followed by a slow addition of 1.15 mL (10 mmol) of 2,3-dimethyl-1,3-butadiene (1.15 mL, 10 mmol). The product was chromatographed (Harrison Chromatotron, eluting with ether-hexanes 1:4) to give 1.21 g (67%) of 4,5-dimethyl-4-cyclohexene-1,2-dicarboxylic anhydride (**19**); mp. 76–77°C (lit. 78–79°C (*39*)) and 0.16 g (8%) 4,5-dimethyl-4-cyclohexene-1,2-dicarboxylic acid (**20**); mp. 199–201°C (d) (lit. 202–203°C (*40*)).

1,3,3a,4,5,7a-Hexahydro-5-methyl-3-oxoisobenzofuran-4-carboxylic acid (21)

A temperature probe, a stirring bar and *trans*, *trans*-2,4-hexadien-1-ol (0.98 g, 10 mmol) were placed in a 10 mL round bottom flask. Water was added (0.70 mL) followed by maleic anhydride (0.98 g, 10 mmol). Stirring was continued for a total of 15 minutes. The solid product was rinsed with a small amount of acetone (2 mL) and left to dry in air. Yield of **21** was 1.90 g (96%); mp. 163–165°C (lit. 161°C (*41*)).

Exo-*3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride (22)*

A temperature probe, a stirring bar and maleic anhydride (29.4 g, 0.30 mol) were placed in a 100 mL round bottom flask. Water was added (10 mL) followed by furan (24.0 mL, 0.30 mol). Stirring was continued for a total of 60 minutes. The solid product was allowed to dry in air and rinsed with a small amount of dichloromethane (10 mL) to give 37.2 g (75%) of *exo*-3,6-epoxy-1,2,3,6-tetrahydrophthalic anhydride (**22**); mp. 110–113°C (d) (lit. 116°C (*37*)).

Acknowledgements

We thank Salvatore Lepore, Department of Chemistry, Florida Atlantic University, for helpful discussions and suggestions and Marc Hill, Wilkes Honors College of Florida Atlantic University, for help in recording reaction temperatures.

References

(1) Imachi, S.; Onaka, M. *Tetrahedron Lett.* **2004,** *45,* 4943–4946.

(2) Fringuelli, F.; Girotti, R.; Pizzo, F.; Vaccaro, L. *Org. Lett.* **2006,** *8,* 2487–2489.

(3) Long, J.; Hu, J.; Shen, X.; Ji. B.; Ding, K. *J. Am. Chem. Soc.* **2002,** *124,* 10–11.

(4) Woodward. R.B.; Baer, H. *J. Am. Chem. Soc.* **1948,** *70,* 1161–1166.

(5) Rideout, D.C.; Breslow, R. *J. Am. Chem. Soc.* **1980,** *102,* 7816–7817.

(6) Breslow, R. *Acc. Chem. Res.* **1991,** *24* (6), 159–164.

(7) Lim, D.; Jenson, C.; Repasky, M.P.; Jorgensen, W.L. In *Transition State Modeling for Catalysis*; Truhlar, D.G., Morokuma, K., Eds.; ACS Symposium Series 721; American Chemical Society: Washington, DC, 1999; pp 79–80.

(8) Grieco, P.A.; Yoshida, K.; Garner, P. *J. Org. Chem.* **1983,** *48,* 3137–3139.

(9) van der Wel, G.K.; Wijnen, J.W.; Engberts, J.B.F.N. *J. Org. Chem.* **1996,** *61,* 9001–9005.

(10) Jung, T.; Marcus, R.A. *J. Am. Chem. Soc.* **2007,** *129,* 5492–5502.

(11) Pirrung, M.C.; Sarma, K.D. *Tetrahedron.* **2005,** *61,* 11456–11472.

(12) Narayan, S.; Muldoon, J.; Finn, M.G.; Fokin, V.V.; Kolb, H.C.; Sharpless, K.B. *Angew. Chem. Int. Ed.* **2005,** *44,* 3275–3279.

(13) Otto, S; Blokzijl, W.; Engberts, J.B.F.N. *J. Org. Chem.* **1994,** *59,* 5372–5376.

(14) Meijer, A.; Otto, S; Engberts, J.B.F.N. *J. Org. Chem.* **1998,** *63,* 8989–8994.

(15) Otto, S.; Engberts, J.B.F.N. *Pure Appl. Chem.* **2000,** *72,* 1365–1372.

(16) Grieco, P.A.; Garner, P.; He, Z. *Tetrahedron Lett.* **1983,** *24,* 1897–1900.

(17) Breslow, R.; Maitra, U.; Rideout, D. *Tetrahedron Lett.* **1983,** *24,* 1901–1904.

(18) Breslow, R.; Maitra, U. *Tetrahedron Lett.* **1984,** *25,* 1239–1240.

(19) am Ende, D.J.; Whritenour, D.C.; Coe, J.W. *Org. Process. Res. Dev.* **2007,** *11,* 1141–1146.

(20) Rothenberg, G.; Downie, A.P.; Raston, C.L.; Scott, J.L. *J. Am. Chem. Soc.* **2001,** *123,* 8701–8708.

(21) Sheppard, W.J. *J. Chem. Educ.* **1963,** *40,* 40–41.

(22) Bourne, J.R. *Org. Process. Res. Dev.* **2003,** *7,* 471–508.

(23) (a) Goodwin, T.E. Presented at the 231st ACS National Meeting of the American Chemical Society, Atlanta, GA, March 26–30, 2006; (b) Goodwin, T.E. *Abstracts of Papers*; American Chemical Society: Washington, DC, 2006; CHED 55.

(24) Cayzer, T.N.; Lilly, M.J.; Williamson, R.M.; Paddon-Row, M.N.; Sherburn, M.S. *Org. Biomol. Chem.* **2005,** *3,* 1302–1307.

(25) Pickering, M. *J. Chem. Educ.* **1990,** *67,* 524–525.

(26) Anastas, P.T.; Warner, J.C. *Green Chemistry: Theory and Practice;* Oxford University Press: Oxford, 1998.

(27) Moffett, R.B. *Org. Synth. Coll.* [Online] **1963,** *4,* 238. http://www.orgsyn.org/orgsyn/pdfs/CV4P0238.pdf (accessed June 17, 2008).

(28) To, K.K.W.; Wang, X.; Yu, C.W.; Ho, Y-P.; Au-Yeung, S.C.F. *Bioorg. Med. Chem.* **2004,** *12,* 4565–4573.

(29) Bigeault, J.; Giordano, L.; De Riggi, I.; Gimbert, Y.; Buono, G. *Org. Lett.* **2007,** *9,* 3567–3570.

(30) Bartlett, P.D.; Roof, A.A.M.; Subramanyam, R.; Winter, W.J. *J. Org. Chem.* **1984,** *49,* 1875–1880.

(31) Russell, G.A.; Whittle, P.R.; Keske, R.G.; Holland, G.; Aubuchon, C. *J. Am. Chem. Soc.* **1972,** *94,* 1693–1698.

(32) Devine, P.N.; Oh, T. *J. Org. Chem.* **1992,** *57,* 396–399.

(33) Demel, S.; Schoefberger, W.; Slugovc, C.; Stelzer, F. *J. Mol. Cat. A: Chem.* **2003,** *200,* 11–19.

(34) Zhu, Z.; Espenson, J.H. *J. Am. Chem. Soc.* **1997,** *119,* 3507–3512.

(35) McDaniel, K.F.; Weekly, R.M. *J. Chem. Educ.* **1997,** *74,* 1465–1467.

(36) McCluskey, A.; Ackland, S.P.; Bowyer, M.C.; Baldwin, M.L.; Garner, J.; Walkom, C.C.; Sakoff, J.A. *Bioorg. Chem.* **2003,** *31,* 68–79.

(37) Leont'eva, S.V.; Manulik, O.S.; Evstigneeva, E.M.; Bobkova, E.N.; Flid, V.R. *Kinet. Catal.* **2006,** *47,* 384–388.

(38) Lowe, Adam J. *Eur. J. Org. Chem.* **2008,** *9,* 1559–1567.

(39) Bailey, W.J.; Rosenberg, J.; Young, L.J. *J. Am. Chem. Soc.* **1954,** *76,* 2251–2254.

(40) (a) Mousseron-Canet, M.; Mousseron, M.; Brown, G. *Rev. Chim. Acad. Rep. Populaire Roumaine.* **1962,** *7,* 1089–1101; (b) Mousseron-Canet, M.; Mousseron, M.; Brown, G. *Chem. Abstr.* **1964,** *61,* 425047.

(41) Brettle, R.; Cummings, D.P. *J. Chem. Soc. Perkin Trans. I.* **1977,** 2385–2392.