Natalie L. Wendt

Class: Senior
Double Major: Biology
and Chemistry

I began my research under the supervision of Dr. Jin Liu in the spring of 2004. Working in the Department of Chemistry at Murray State University has provided me with both hands-on experience and the opportunity to study new and exciting chemistry. We have been synthesizing cisoid molecules, working to isolate isomers of these compounds. As a result of our work, Dr. Liu and I were able to determine the critical conditions under which the photo-conversion occurs. When I am not in the lab or studying, I spend my time with the MSU rowing team, playing softball or running.

ABSTRACT

Synthesis of Cisoid 1-Alkyl-1,4-diphenyl-1,3-butadienes

Photoirradiation of 1-Alkyl-1,4-diphenyl-1,3-butadienes was found to induce photoisomerization of the compounds. UV irradiation of 1-methyl-1,4-diphenyl-1,3-butadiene yields two isomers (1*E*, 3*E*) and (1*Z*, 3*E*), however, upon irradiation of 1-trifluoromethyl-1,4-diphenyl-1,3-butadiene only the (1*Z*, 3*E*) isomer was formed. Our observations suggest that the alkyl substituent effects the regioselectivity of the compound. An electron donating group, such as the methyl group, decreases the regioselectivity, and an electron withdrawing group, such as the trifluoromethyl group, increases the regioselectivity of the compound.

FACULTY MENTOR

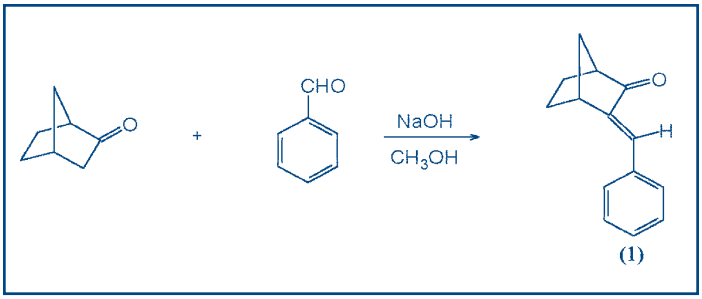
Jin Liu, who is in her fifth year at Murray State University, came to the Department of Chemistry after obtaining a Ph.D. at the University of Hawaii and completing a postdoctoral research appointment at Cornell University. Her teaching interests include organic chemistry, polymer chemistry and brief organic chemistry. Wendt is one of over 15 students whom Liu has mentored in her bioorganic chemistry laboratory.

Synthesis of Cisoid 1-Alkyl-1,4-diphenyl-1,3-butadienes

Introduction

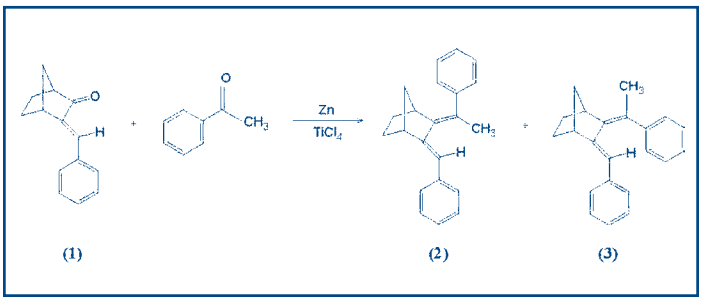
Photoisomerization of symmetrical cisoid 1,4-diphenyl-1,3-butadienes gives only one (*E*,*Z*)-isomer because of the equivalence of the two aryl groups. However, photoisomerization will produce two different isomers, (1*Z*,3*E*) and (1*E*,3*Z*), when the two aryl groups are not symmetrical (Liu, Suits, and Boarman, 2003). Previous experiments show that direct irradiation of the (1*E*,3*E*) isomers of fluorinated cisoid 1,4-diphenyl-1,3-butadienes in an organic solvent will lead to formation of the major (1*Z*,3*E*) isomers (Liu, Suits, and Boarman, 2003). Unique regioselectivity upon photoisomerization has been indicated in the previous study. The purpose of this research project was to determine whether photoirradiation of the (1*E*,3*E*) isomers of 1-alkyl-1,4-diphenyl-1,3-butadienes would produce the (1*Z*,3*E*) and/or (1*E*,3*Z*) isomers. To determine the effects of the substituents upon photoisomerization, an electron withdrawing group (-CF_3) and an electron donating group (-CH_3) were introduced to the butadiene system.

In order to study the photoisomerization of (*E*,*E*)-1-alkyl-1,4-diphenyl-1,3-butadienes, the compounds (**1**-**5**) were synthesized. First, to synthesize the desired substituted enone (**1**), an aldol condensation reaction was used. To couple the molecules, a strong base (sodium hydroxide in methanol) was used to treat a ketone and an aldehyde. The general synthetic approach for the Aldol condensation is shown in Scheme 1. The approach is dependent on the presence of alpha hydrogens on the norcamphor molecule. The use of the strong base removed one of the alpha hydrogens from norcamphor, and the resulting sodium enolate was used, as the nucleophile, to attack the carbonyl carbon of the aldehyde. The final product of this first reaction was a phenyl-substituted enone (**1**). Next, the McMurray Coupling reaction, which has proven to be successful in the synthesis of cisoid 1,4-diphenyl-1,3-butadienes, was used to introduce the second phenyl ring (Liu, Suits, and Boarman, 2003; Liu, Murray, and Young, 2003).



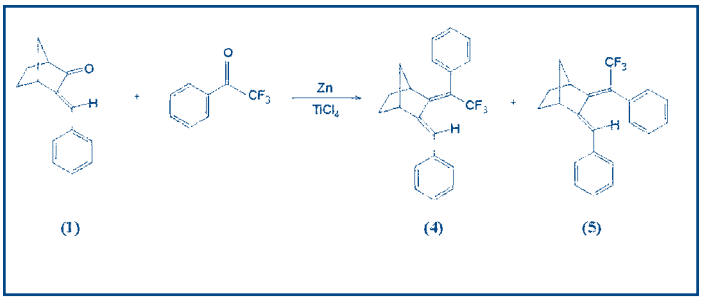
Scheme 1. Synthesis of the phenyl-substituted enone (**1**)

The McMurray Coupling reaction is a dimerization and a reduction of ketones mediated by a Titanium reagent. The reaction involves the reduction of the ketones first. Then, the deoxygenation of the molecule affords the desired product. During the deoxygenation, a carbon-carbon double bond between the two ketone molecules is formed. The phenyl-substituted enone (**1**) was used to synthesize the desired (*E*,*E*)-1-alkyl-1,4-diphenyl-1,3-butadiene by using a McMurray Coupling reaction. Scheme 2 shows the synthetic approach used for the preparation of compounds (**2**) and (**3**).



Scheme 2. McMurray Coupling of the phenyl-substituted enone (**1**) and acetophenone

Also, Scheme 3 shows the similar synthetic approach used to prepare compounds (**4**) and (**5**). However, compound **5** was the only isomer isolated from the synthetic mixture.



Scheme 3. McMurray Coupling of the phenyl-substituted enone (**1**) and trifluoroacetophenone

Experimental Procedures

*Preparation of Compound **1**:*

The preparation of the enone was accomplished by adding benzaldehyde (1.74 g, 0.0164 mol) and norcamphor (1.8 g, 0.0164 mol) to a solution of sodium hydroxide (0.6 g, 0.0150 mol) in methanol (6 mL). The reaction mixture was stirred for three hours at room temperature and then quenched by the slow addition of water (15 mL). The reaction mixture was then extracted by ethyl ether three times. The combined ether layers were washed with water and brine, and then dried over $MgSO_4$. The solvent was evaporated, and the product was obtained. Column chromatography was then used to isolate the pure product, and a thin-line chromatography (TLC) was performed to determine which test tubes contained the product. The test tubes containing the product were combined, and the solvent was evaporated.

*Preparation of Compounds **2** and **3**:*

The preparation of (*E*,*E*)-1,alkyl-1,4-diphenyl-1,3-butadiene was accomplished by using a McMurray Coupling reaction. This was done using a titanium reagent. Activated zinc dust (0.7 g, 0.01071 mol) in THF (3mL) was added to a round bottom flask. The reaction flask was placed in an ice bath and cooled to 0 ºC. A syringe was then used to syringe $TiCl_4$ (5 mL, 1.0 M, 0.005 mol) into the flask. The reaction mixture was heated at reflux for 30 minutes. Pyridine (two drops) was added via a syringe. Next, a solution of enone (**1**) (0.6 g, 3.2 mmol) and benzaldehyde (0.48 g, 4 mmol) was added to the round bottom flask. Reflux was continued for two hours and 20 minutes. The reaction was quenched with water (15 mL) and extracted with ethyl ether. The organic layers were then washed with brine and dried. The compound was purified by silica gel chromatography using hexanes as the solvent. Thin-line chromatography (TLC) was used to determine the separation of the isomers. The test tubes containing the product were combined, and the solvent was evaporated. The isomers were identified using NMR spectroscopy.

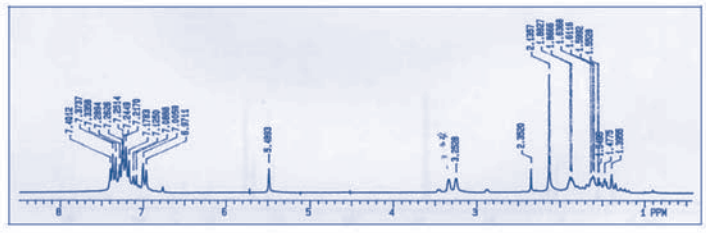


Figure 5: ^{1}H-NMR spectrum of compounds **2** and **3**

*Compound **2** –* ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.20-1.80 (m, 4H), 2.13 (s, 3H), 2.88 (s, 1H), 3.45 (s, 1H), 6.78 (s, 1H, vinylic), 6.90-7.40 (m, 10H, aromatic).

*Compound **2** –* ^{13}C-NMR (50.1 MHz, $CDCl_3$) δ: 25.1, 30.9, 30.1, 42.8, 45.1, 45.6, 125.0, 148.0.

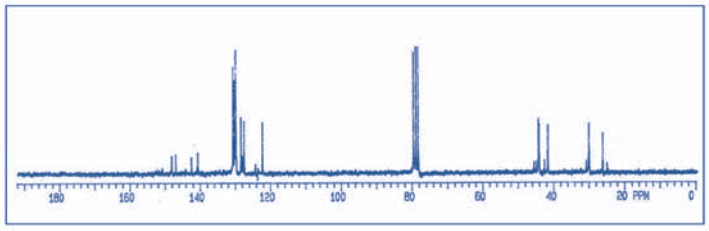


Figure 6: ^{13}C-NMR spectrum of compounds **2** and **3**

*Compound **3** –* ^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.40-1.90 (m, 4H), 2.35 (s, 3H), 3.26 (s, 1H), 3.34 (s, 1H), 5.50 (s, 1H, vinylic), 6.90-7.40 (m, 10H, aromatic).

*Compound **3** –* ^{13}C-NMR (50.1 MHz, $CDCl_3$) δ: 26.3, 30.0, 30.1, 41.8, 44.3, 44.4, 125.0, 148.0.

*Preparation of Compound **5**:*

The preparation of compound (**5**) was accomplished using the McMurray Coupling reaction. A solution of activated zinc dust (0.7 g, 0.0107 mol) in THF (3 mL) was added to a round bottom flask. The flask was placed in an ice water bath and cooled to

0 ºC. A syringe was used to syringe $TiCl_4$ (5 mL, 1 M, 0.005 mol) into the reaction flask, and the reaction was heated at reflux for 30 minutes. Pyridine (two drops) was added to the reaction flask. Next, the enone (**1**) (0.73 g, 3.69 mmol) and trifluoroacetophenone (0.7 g, 4 mmol) were added to the reaction. The reaction was then heated at reflux for three hours and 40 minutes. Column chromatography was used to separate the isomers, and any remaining starting material. This was done using a long column with hexanes as the solvent. The test tubes containing the desired product were combined, and the solvent was evaporated. The isomers were then identified using NMR spectroscopy.

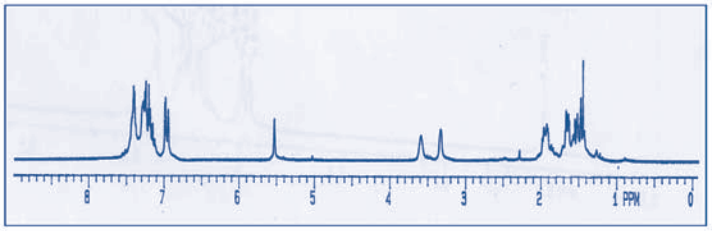


Figure 7: ^{1}H-NMR spectrum of compound **5**

^{1}H-NMR (200 MHz, $CDCl_3$) δ: 1.40-1.70 (m, 4H), 1.90-2.00 (m, 2H), 3.30 (s, 1H), 3.60 (s, 1H), 5.50 (s, 1H, vinylic), 6.90-7.40 (m, 10H, aromatic).

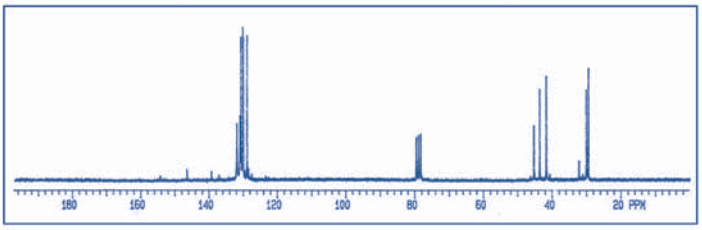


Figure 8: ^{13}C-NMR spectrum of compound **5**

^{13}C-NMR (50.1 MHz, $CDCl_3$) δ: 29.6, 30.1, 41.8, 43.7, 45.4, 128.5, 128.9, 129.6, 130.1, 130.3, 130.5, 130.8, 131.0, 131.9, 139.4, 146.6

Computational Results

The computational NMR data allowed us to determine that two isomers were formed upon synthesis of 1-methyl-1,4-diphenyl-1,3-butadiene. However, only one isomer of 1-trifluoromethyl-1,4-diphenyl-1,3-butadiene was formed. The major isomers are shown by the peaks with high intensity, and the minor isomers that are formed are represented by the low intensity peaks.

The experimental and computational data was then used to assign NMR peaks to the corresponding isomers of the 1-alkyl-1,4-diphenyl-1,3-butadienes (Kong et. al, 2000). The vinylic hydrogen for the (1*E*,3*E*)-1-methyl-1,4-diphenyl-1,3-butadiene shows a chemical shift of 6.8 ppm, and the vinylic hydrogen for the (1*Z*,3*E*)-1-methyl-1,4-diphenyl-1,3-butadiene shows a chemical shift of 5.5 ppm. Also, the chemical shifts of the two bridgehead hydrogens are different for the two isomers. The chemical shifts at 3.2 ppm and 3.3 ppm are consistent with the presence of (1*Z*,3*E*)-1-methyl-1,4-diphenyl-1,3-butadiene, and shifts at 2.9 ppm and 3.4 ppm are consistent with the presence of (1*E*,3*E*)-1-methyl-1,4-diphenyl-1,3-butadiene. Tables 1-4 show the calculated chemical shifts in the ^{1}H-NMR and ^{13}C-NMR spectra for compounds (**2-5**)**.** Analysis of these data shows that the major isomers formed are the (1*Z*,3*E*) isomers of the 1-alkyl-1,4-diphenyl-1,3-butadienes. The minor isomer (1*E*,3*E*)-1-methyl-1,4-diphenyl-1,3-butadienes is formed, but close examination of the data shows that the (1*E*,3*E*)-1-trifluoromethyl-1,4-diphenyl-1,3-butadiene, compound (**4**), was not formed. Figure 9 shows the optimized structures of compounds **2-5**, based on the computational results.

Table 1

Chemical shifts of (1*E*,3*E*)-1-methyl-1,4-diphenyl-1,3-butadiene (Kong et. al., 2000)

NMR shifts (ppm)	Atom	Isotropic	Rel. Shift
1	C1	98.3325	114.862
2	H3	27.0583	6.560
3	C2	76.1745	137.020
4	C3	81.7414	131.453
5	C4	91.4490	121.745
6	C5	177.1379	36.056
7	H8	31.1276	2.491
8	C6	176.9240	36.270
9	H11	31.5934	2.025
10	C7	190.6815	22.513
11	H12	32.2294	1.389
12	H13	32.3721	1.246
13	C8	187.5337	25.661
14	H14	32.5658	1.052
15	H15	32.4503	1.168
16	C9	179.9939	33.200
17	H9	32.6037	1.014
18	H10	32.7660	0.852
19	C10	84.1490	129.045
20	C11	95.4176	117.777
21	C12	93.2738	119.921
22	C13	92.6977	120.497
23	C14	93.8897	119.305
24	C15	93.8231	119.371
25	H6	26.2375	7.381
26	H16	26.2449	7.373
27	H17	26.2402	7.378
28	H18	26.3512	7.267
29	C16	76.4557	136.739
30	C17	95.6816	117.513
31	C18	94.6116	118.583
32	C19	93.0993	120.095
33	C20	93.3960	119.798
34	C21	93.0502	120.144
35	H20	26.2285	7.390
36	H21	26.1936	7.424
37	H22	26.3228	7.295
38	H1	26.3470	7.271
39	H2	26.4088	7.209
40	H25	26.3246	7.293
41	C22	190.8948	22.300
42	H4	31.2328	2.385
43	H5	31.3443	2.274
44	H7	31.9782	1.640

Table 2

Chemical shifts of (1*Z*,3*E*)-1-methyl-1,4-diphenyl-1,3-butadiene (Kong et. al., 2000)

NMR shifts (ppm)	Atom	Isotropic	Rel. Shift
1	C1	98.0567	115.138
2	H3	28.4130	5.205
3	C2	80.0083	133.186
4	C3	84.4815	128.713
5	C4	93.8959	119.298
6	C5	177.9536	35.241
7	H8	31.2236	2.394
8	C6	177.4758	35.719
9	H11	31.0623	2.556
10	C7	189.1082	24.086
11	H12	32.1003	1.518
12	H13	32.3136	1.304
13	C8	188.4002	24.794
14	H14	32.3226	1.295
15	H15	32.0970	1.521
16	C9	180.4843	32.710
17	H9	32.5665	1.052
18	H10	32.6007	1.017
19	C10	84.1353	129.059
20	C11	95.9793	117.215
21	C12	93.3952	119.799
22	C13	93.6709	119.523
23	C14	94.3794	118.815
24	C15	94.2801	118.914
25	H6	26.4964	7.122
26	H16	26.4172	7.201
27	H17	26.5020	7.116
28	H18	26.5422	7.076
29	C16	79.0570	134.137
30	C17	95.4774	117.717
31	C18	93.3562	119.838
32	C19	93.7869	119.407
33	C20	92.4112	120.783
34	C21	93.1042	120.090
35	H20	26.2219	7.396
36	H21	26.1296	7.489
37	H22	26.3252	7.293
38	H1	26.2393	7.379
39	H2	26.9712	6.647
40	H25	26.3249	7.293
41	C22	189.6410	23.553
42	H4	31.4928	2.125
43	H5	31.7793	1.839
44	H7	31.7367	1.881

Table 3

Chemical shifts of (1*E*,3*E*)-1-trifluoromethyl-1,4-diphenyl-1,3-butadiene (Kong et. al, 2000)

NMR shifts (ppm)	Atom	Isotropic	Rel. Shift
1	C1	89.2051	123.989
2	H3	25.9724	7.646
3	C2	84.4330	128.761
4	C3	63.8468	149.347
5	C4	103.8781	109.316
6	C5	177.5312	35.663
7	H8	31.0407	2.577
8	C6	175.0410	38.153
9	H11	31.5723	2.046
10	C7	190.7523	22.442
11	H12	32.1497	1.468
12	H13	32.2236	1.394
13	C8	188.6622	24.532
14	H14	32.5746	1.044
15	H15	32.3505	1.268
16	C9	180.9949	32.199
17	H9	32.6198	0.998
18	H10	32.7170	0.901
19	C10	85.6542	127.540
20	C11	94.1308	119.064
21	C12	92.6547	120.540
22	C13	92.6387	120.556
23	C14	94.0730	119.121
24	C15	93.8916	119.303
25	H6	26.1853	7.433
26	H16	26.2064	7.412
27	H17	26.2006	7.417
28	H18	26.2612	7.357
29	C16	85.4779	127.716
30	C17	93.6251	119.569
31	C18	90.4611	122.733
32	C19	90.7578	122.437
33	C20	93.6578	119.536
34	C21	93.7355	119.459
35	H20	26.1677	7.450
36	H21	26.1560	7.462
37	H22	26.1742	7.444
38	H1	26.1669	7.451
39	H2	26.3101	7.308
40	H25	26.2265	7.392
41	C22	101.0020	112.192
42	F1	334.1438	
43	F2	315.4584	
44	F3	334.5811	

Table 4

Chemical shifts of (1*Z*,3*E*)-1-trifluoromethyl-1,4-diphenyl-1,3-butadiene (Kong et. al., 2000)

NMR shifts (ppm)	Atom	Isotropic	Rel. Shift
1	C1	91.0443	122.150
2	H3	28.0332	5.585
3	C2	83.1406	130.054
4	C3	66.2373	146.957
5	C4	102.5072	110.687
6	C5	178.2440	34.950
7	H8	31.1501	2.468
8	C6	175.9648	37.230
9	H11	30.5487	3.069
10	C7	189.7356	23.459
11	H12	32.0510	1.567
12	H13	32.3323	1.286
13	C8	188.8846	24.310
14	H14	32.1383	1.480
15	H15	31.9088	1.709
16	C9	180.7217	32.473
17	H9	32.5144	1.104
18	H10	32.4782	1.140
19	C10	86.0585	127.136
20	C11	94.4865	118.708
21	C12	93.0592	120.135
22	C13	93.5009	119.693
23	C14	94.2402	118.954
24	C15	94.1305	119.064
25	H6	26.4188	7.199
26	H16	26.3393	7.279
27	H17	26.4299	7.188
28	H18	26.4137	7.204
29	C16	87.2662	125.928
30	C17	93.3162	119.878
31	C18	90.4864	122.708
32	C19	91.0813	122.113
33	C20	92.7240	120.470
34	C21	93.3469	119.847
35	H20	26.1683	7.450
36	H21	26.0609	7.557
37	H22	26.1684	7.450
38	H1	26.0922	7.526
39	H2	26.9379	6.680
40	H25	26.2054	7.413
41	C22	100.4247	112.770
42	F1	338.7338	
43	F2	324.6291	
44	F3	327.0695	

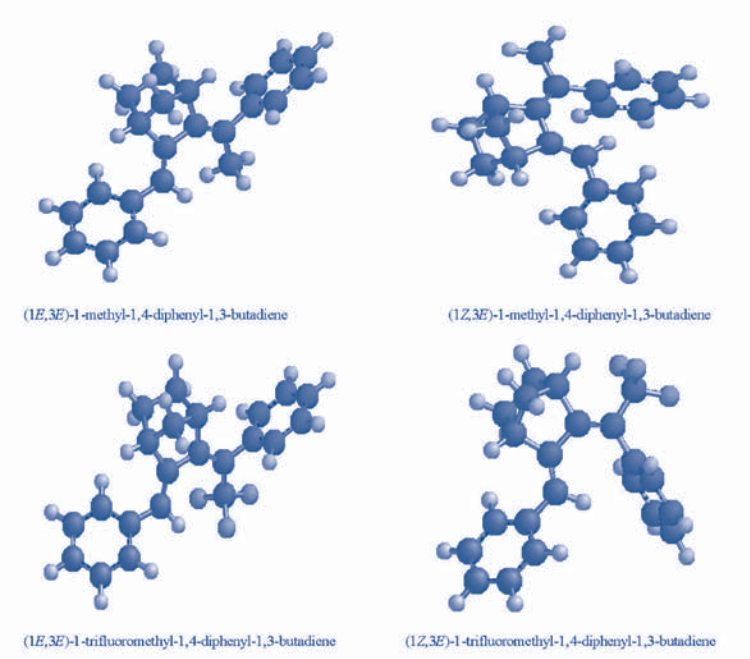
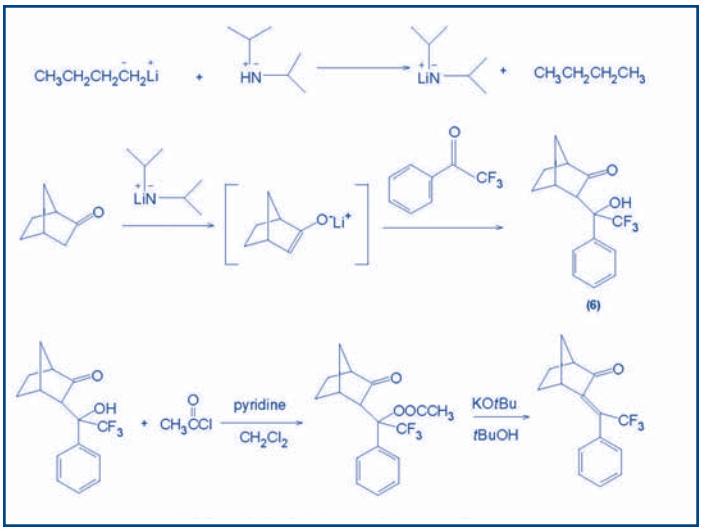


Figure 9: The optimized structures **(2-5)** determined by way of HF-6-31G



Scheme 4: An alternative synthetic approach

Results and Discussion

In order to prepare (1*E*,3*E*)-1-trifluoromethyl-1,4-diphenyl-1,3-butadiene, a different synthetic approach was attempted. The first step in that synthesis is to prepare compound **6**. This was done by addition of butyllithium to diisopropyl amine to form lithium diisopropyl amine (LDA), which was then reacted with norcamphor to form the lithium enolate intermediate. The enolate intermediate was reacted with trifluoroacetaphenone to produce compound **6,** which was successfully isolated (Scheme 4). This product is supposed to undergo an acylation with acetyl chloride in pyridine, as a catalyst, and dichloromethane as a solvent to protect the hydroxyl group. Then, potassium *tert*-butoxide (KO*t*Bu) in THF can be used in the attempt to form a double bond. However, the acylation reaction afforded a side product, due to the effect of the nearby fluorine. An alternative approach for protecting the hydroxyl group is certainly needed for the completion of the proposed dehydration step.

The reason why two isomers were formed upon synthesis of 1-methyl-1,4-diphenyl-1,3-butadiene, (1*E*,3*E*) and (1*Z*,3*E*), yet only one isomer, (1*Z*,3*E*), was formed upon synthesis of 1-trifluoromethyl-1,4-diphenyl-1,3-butadiene is still under investigation. Prior to interpreting the NMR data, it was hypothesized that (1*E*,3*E*)-1-trifluoromethyl-1,4-diphenyl-1,3-butadiene would be the major isomer for this compound. We believed the (1*E*,3*E*) isomer would be the major isomer because hydrogen bonding between the fluorine and the hydrogen in the structure would make the compound more stable. However, the data that we collected and analyzed shows that the (1*Z*,3*E*) isomer is the major isomer that was formed. We currently believe that steric hinderance may play a critical role in the formation of the (1*E*,3*E*) isomer.

According to the previous studies conducted in the same lab, an electron donating group will strengthen the carbon-carbon double bond. By strengthening this double bond, the observed regioselectivity is decreased upon photoirradiation. If an electron withdrawing substituent, such as fluorine, is attached to the phenyl ring, which is attached to the carbon-carbon double bond, an increase in regioselectivity is observed. The electron withdrawing group allows for the formation of the major (1*Z*,3*E*) isomer and increases the selectivity upon photoirradiation (Liu, Suits, and Boarman, 2003; Liu, Murray, and Young, 2003). Upon irradiation of the compounds (**3** and **5**), photoisomerization of the compounds (**2, 3** and **5**) was not observed. The compounds appear to undergo a photocyclization process. The mechanism of this photo-reaction is under current investigation.

References

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