ORGANIC
LETTERS

2006
Vol. 8, No. 24
5561−5564

Microwave-Assisted Regioselective Cycloaddition Reactions between 9-Substituted Anthracenes and Levoglucosenone

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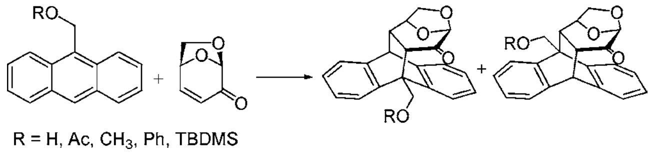
Received September 11, 2006

ABSTRACT

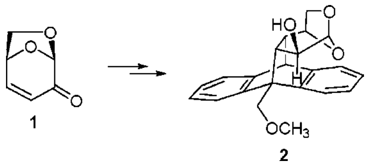


The cycloaddition reactions of 9-substituted anthracenes and levoglucosenone were investigated under microwave irradiation and conventional heating conditions. Considering time, yields, and regioselectivity, microwave technology has proven to be an ideal tool to achieve this chemical transformation.

Levoglucosenone (1,6-anhydro-3,4-dideoxy-*β*-D-glycero-hex-3-enopyranos-2-ulose or (1*S*,5*R*)-6,8-dioxabicyclo[3.2.1]oct-2-en-4-one) (**1**) is a versatile and readily available member of the carbohydrate-derived chiral pool. The synthesis of **1** is most efficiently accomplished by the pyrolysis of cellulose or cellulose-containing material such as waste paper.[1] Levoglucosenone possesses several features that make it an attractive chiral raw material for the synthesis of a wide variety of compounds.[2] As part of our program on the pyrolytic conversion of biomass into useful chemicals, we have been concerned with the synthetic application of levoglucosenone as a chiral building block in the development of new tools for asymmetric synthesis.[3]

The Diels−Alder reaction has been among the most popular and successful synthetic applications of carbohydrate auxiliaries, especially when they are attached to the dienophile. Recently, we have reported the design and synthesis of alcohol **2** derived from levoglucosenone (Scheme 1) and its use as a chiral inductor in Diels−Alder reactions of the corresponding acrylate with cyclopentadiene yielding the product with 98% diastereomeric excess.[4]

Scheme 1



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(1) (a) Witczak, Z. J., Ed. *Levoglucosenone and Levoglucosans: Chemistry and Applications*; ATL Press: Mount Prospect, 1994. (b) Witczak, Z. J.; Tatsuta, K., Eds. *Carbohydrate Synthons in Natural Products Chemistry. Synthesis, Functionalization, and Applications.* ACS Symposium Series 841; American Chemical Society: Washington, DC, 2003.

(2) For examples, see: (a) Nishikawa, T.; Urabe, D.; Isobe, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 4782. (b) Gómez, M.; Quincoces, J.; Peseke, K.; Michalik, M.; Reinke, H. *J. Carbohydr. Chem.* **1999**, *18*, 851. (c) Swenton, J. S.; Freskos, J. N.; Dalidowicz, P.; Kerns, M. L. *J. Org. Chem.* **1996**, *61*, 459.

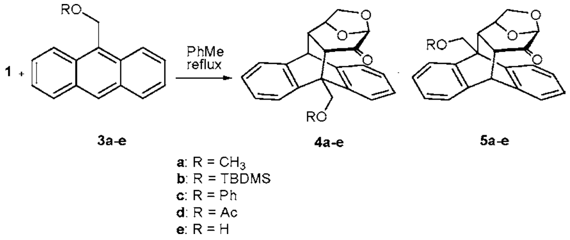
10.1021/ol062254g CCC: $33.50

Attempts to improve the π-facial diastereoselectivity in this cycloaddition reaction led us to envisage new chiral auxiliaries derived from levoglucosenone. Different substituents at the benzylic position would introduce a new element of steric control, therefore imposing greater restrictions to the transition state.

The key step to obtain the chiral auxiliaries was a Diels–Alder reaction between levoglucosenone and the aromatic dienes. Our approach for the design of new molecular scaffolds relied on the use of suitable 9-substituted anthracene derivatives **3** (easily prepared from commercially available 9-anthracenemethanol or anthracen-9-ylmethanol) as the source of molecular diversity to tune the efficiency of the asymmetric inductor.

Cycloaddition reactions of **1** with **3a**–**e** would be expected to yield up to four isomeric products because the aromatic substrate can add from the bottom or the top face of the dienophile. However, after column chromatography to remove the excess of the diene, only one or two regioisomers were isolated depending on the diene employed (Scheme 2).

Scheme 2



The stereochemical assignments of the new compounds were based on ^{1}H NMR spin decoupling and NOE data. All the reactions afforded the adducts derived from the diene approach opposite to the 1,6-anhydro bridge of **1**. Adducts **4a**–**e** and **5a**–**e** were identified as the ortho and meta regioisomers, respectively.

The failure of the cycloaddition reactions performed with Lewis acid catalysis (such as $FeCl_3$, $ScTf_3$, $AlCl_3$, $LiClO_4$, and $BF_3{\cdot}OEt_2$) prompted us to carry out the Diels–Alder reaction under thermal conditions (Table 1).

Table 1. Cycloaddition Reaction of **1** with **3** in Refluxing Toluene

entry	diene **3**: R	time (days)	yield (%)[a]	ortho/meta
1	**a**: Me	7	100	88:12
2	**b**: TBDMS	10	92	85:15
3	**c**: Ph	7	75	100:0
4	**d**: Ac	6	82	100:0
5	**e**: H	12	47	100:0

[a] Yield corresponds to isolated products.

As shown in Table 1, the yield and selectivity of the cycloaddition reaction varied with the reagent employed. In general, the products were obtained in good to excellent yields with high ortho selectivity.[5] It was already observed that the ortho product is generally preferred in cycloaddition reactions in which 9-substituted anthracenes are used as dienes.[6,7]

Regardless of the good yields and selectivities observed in these cycloadditions, all the reactions needed long reaction times (between 6 and 12 days) to obtain good conversion of the starting material. For this reason, the use of a microwave-assisted cycloaddition procedure was considered to improve the outcome of these reactions. This approach would save energy by shortening the reaction time and also by making the overall process more efficient and sustainable. Diels–Alder cycloadditions were the first reaction types to be examined in conjunction with microwave irradiation, and these conditions reduced significantly the reaction times compared to conventional heating methods.[8]

To make a systematic study of the different variables involved in these microwave-irradiated cycloaddition reactions, we decided to study the reaction of **3a** with levoglucosenone. This substrate was selected among the others because it was shown to give both good yields and regioselectivity under thermal conditions. The assays were performed at 150 W in different solvents because solvents are a crucial factor in the outcome of the reaction.[9] The solvents were chosen to compare a selection that included high and low microwave energy absorbers. A key feature of these microwave-assisted reactions was the reagent concentration. The reaction only proceeded with a dienophile concentration of 1.5 M that involved solutions 8 times more concentrated than the ones used under conventional heating. Table 2 shows the cycloaddition reactions of **1** with **3a** performed in a pressurized environment.

Table 2. Cycloaddition Reactions of **1** (1.5 M) with **3a** at 150 W for 10 min

entry	solvent	temp (°C)	yield (%)[a]	ortho/meta
1	xylene	170	54	60:40
2	DMF	170[b]	43	32:68
3	CyHex	155	41	82:18
4	THF	165	47	83:17
5	MTBE	140	50	52:48
6	MeCN	146	22	84:16
7	EtOH	140	20	86:14
8	H_2O	130	29	86:14

[a] Yield corresponds to isolated products. [b] Performed under controlled temperature at 170 °C.

The experimental data shown in Table 2 demonstrate that the best results, considering yield and ortho/meta selectivity, were obtained when employing cyclohexane or THF. With

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(3) (a) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G. *Tetrahedron Lett.* **2004**, *45*, 8203. (b) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G. *Tetrahedron Lett.* **2005**, *46*, 6987.

(4) Sarotti, A. M.; Spanevello, R. A.; Suárez, A. G. *Org. Lett.* **2006**, *8*, 1487.

polar solvents (entries 6−8), the selectivities obtained were good but the yields were very low. On the other hand, solvents such as xylene (entry 1) or MTBE (entry 5) gave the best yields but very low ortho/meta ratio. These results led us to make a more detailed experimental study using THF and cyclohexane. We analyzed the effects of varying diene equivalents, microwave power, and reaction time on the outcome of the Diels−Alder reaction. Table 3 shows the results of the microwave-assisted cycloaddition reaction of **1** with **3a**−**e** under different experimental conditions and a registered reaction temperature between 155 and 165 °C. The analysis of these results demonstrates that an increment in the equivalent of diene produces better yields. When the reaction time is increased, the selectivity toward the ortho regioisomer decreases. In some cases, the selectivity reverts giving the meta adduct as the major product. This effect can be attributed to the retro Diels−Alder reaction of the initially formed ortho isomer, which is the thermodynamically less stable adduct.

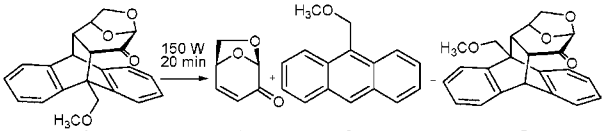
Table 3. Cycloaddition Reaction of **1** with **3a**−**e** at 150 W

entry	diene **3**: R (equiv)	solvent	time (min)	yield (%)[a]	ortho/meta
1	**a**: Me (2)	CyHex	10	41	82:18
2	**a**: Me (2)	CyHex	20	67	71:29
3	**a**: Me (2)	THF	10	47	83:17
4	**a**: Me (2)	THF	30	54	27:73
5	**a**: Me (3)	THF	10	62	73:27
6	**b**: TBDMS (2)	CyHex	10	40	80:20
7	**b**: TBDMS (2)	CyHex	20	57	78:22
8	**b**: TBDMS (2)	THF	10	47	77:23
9	**b**: TBDMS (2)	THF	20	58	69:31
10	**b**: TBDMS (2)	THF	50	57	24:76
11	**b**: TBDMS (2)	THF	10	57	90:10
12	**c**: Ph (2)	CyHex	10	−[b]	−
13	**c**: Ph (2)	THF	10	−[b]	−
14	**d**: Ac (2)	CyHex	20	38	41:59
15	**d**: Ac (3)	THF	10	34	41:59
16	**e**: H (2)	CyHex	20	31	33:77
17	**a**: H (3)	THF	10	53	92:8

[a] Yield corresponds to isolated products. [b] Compound **3c** decomposes at 150 W.

To test the possibility of a retro Diels−Alder mechanism, we subjected a THF solution of pure **4a** to microwave irradiation at 150 W for 20 min. The reaction produced a mixture of meta isomer **5a**, levoglucosenone (**1**), and 9-(methoxymethyl)anthracene (**3a**) (Scheme 3).

Scheme 3



The ortho isomer undergoes a retro Diels−Alder reaction leading to the formation of the thermodynamically more stable meta isomer. This experimental evidence explains the results shown in Table 3: longer reaction times produce better yields but reduce the ortho selectivity.

We also demonstrated experimentally that the retro Diels−Alder reaction did not take place under conventional thermal conditions. The reaction of **1** with **3a** or **3b** was carried out in refluxing toluene, and the reaction mixture was controlled by ^{1}H NMR every 48 h. The results obtained showed that the yield increased with time and the regioselectivity remained constant. Moreover, ortho adducts **4a** or **4b** were refluxed under toluene during 192 h and the starting materials were recovered quantitatively.

Hitherto, microwave conditions produced an important acceleration of the reaction rate that could be rationalized in terms of thermal effects and increased concentration of the reagents. Under these conditions, it is also possible to observe the reversibility of the cycloaddition process to form the thermodynamically more stable meta adduct.[10]

To optimize yields and selectivities in this cycloaddition process, we investigated the effect of applying lower microwave irradiation power. The quantity of the applied energy should be high enough to obtain good conversion in a reasonable period of time but, on the other hand, low enough to avoid or at least minimize the retro Diels−Alder path. Table 4 describes the results of the cycloaddition

Table 4. Cycloaddition Reaction of **1** with **3a**−**e** in THF

entry	diene **3**: R (2 equiv)	power (W)	time (min)	yield (%)[a]	ortho/meta
1	**a**: Me	100	30	44	85:15
2	**a**: Me	100	60	58	81:19
3	**a**: Me	100	90	75	76:24
4	**a**: Me	50	180	70	85:15
5	**a**: Me	50	240	80	79:21
6	**a**: Me	50	300	82	74:26
7	**b**: TBDMS	100	30	45	92:8
8	**b**: TBDMS	100	60	69	76:24
9	**b**: TBDMS	100	90	75	43:57
10	**b**: TBDMS	50	180	65	86:14
11	**b**: TBDMS	50	240	75	85:15
12	**b**: TBDMS	50	300	79	75:25
13	**c**: Ph	100	30	−[b]	−
14	**c**: Ph	50	180	60	100:0
15	**c**: Ph	50	240	65	100:0
16	**c**: Ph	50	300	67	100:0
17	**d**: Ac	100	30	31	49:51
18	**d**: Ac	100	60	52	38:62
19	**d**: Ac	100	90	60	35:65
20	**d**: Ac	50	180	57	88:12
21	**d**: Ac	50	240	67	75:25
22	**e**: H	100	30	43	68:32
23	**e**: H	100	60	56	68:32
24	**e**: H	100	90	70	67:33
25	**e**: H	50	180	65	85:15
26	**e**: H	50	240	71	85:15

[a] Yield corresponds to isolated products. [b] Compound **3c** decomposes at 100 W.

reactions under 100 or 50 W of irradiation power. Under these experimental conditions, the registered reaction temperature was 125 and 95 °C, respectively.

The experimental results show that in general the yields and selectivity were improved under low-power microwave irradiation. The best results for all dienes studied were obtained in 240 min at 50 W. It is important to mention that even under low irradiation conditions the selectivity for dienes **3a** and **3b** decreased with time. This observation may be explained if we consider that the retro Diels−Alder process is not completely inhibited under the conditions employed. Noticeably, the ortho/meta ratio for dienes **3d** and **3e** did not change with time, indicating that under these experimental conditions the retro Diels−Alder reaction was not observed. Comparing the results obtained under conventional heating (Table 1) and microwave conditions (Table 4), we found that microwave-assisted reactions occurred at 50 times higher reaction rates but also proceeded with 8 times more concentrated solutions. In general, the products are obtained in similar selectivities and only slightly lower yields, compared to the thermal conditions.

In conclusion, we developed a microwave-assisted procedure to prepare adducts derived from levoglucosenone and 9-substituted anthracenes in good yields and selectivities. The methodology allows us to control the regioselectivity by modifying the experimental conditions. We believe that microwave techniques are a suitable approach to obtain chiral auxiliaries from biomass under mild and efficient conditions.

Acknowledgment. This research was supported by Agencia Nacional de Promoción Científica y Tecnológica, Argentina, the International Foundation for Science, Sweden, and the Organization for the Prohibition of Chemical Weapons, The Netherlands. A.M.S. thanks CONICET and Fundación Josefina Prats for the award of a fellowship. Thanks are also due to Wyeth Research and NSF for an internship.

Supporting Information Available: Experimental procedures for the synthesis of all compounds, characterization data, and copies of ^{1}H and ^{13}C NMR spectra of new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(5) The ortho adduct **4e** is obtained as a mixture of the free carbonyl compound and the corresponding intramolecular hemiketal derivative. As both products are in equilibrium, it was not possible to separate the mixture. The structure elucidation was achieved by acetylation of the mixture and subsequent separation of each component (see Supporting Information).

(6) (a) Fringuelli, F.; Taticchi, A. *Dienes in the Diels−Alder Reaction*; John Wiley & Sons: New York, 1990; Chapter 6. (b) Atherton, J. C. C.; Jones, S. *Tetrahedron* **2003**, *59*, 9039.

(7) (a) The preference for meta regioselectivity in Diels−Alder reactions of 9-substituted anthracenes and 2-acetamidoacrylate under forcing conventional heating or microwave irradiation conditions was reported recently.[6b] However, this regioselectivity was achieved at the expense of the overall yield of the reaction. (b) Yang, B. V.; Doweyco, L. D. *Tetrahedron Lett*. **2005**, *46*, 2857.

(8) (a) Hayes, B. L. *Microwave Synthesis. Chemistry at the Speed of Light*; CEM Publishing: Matthews, NC, 2002; Chapter 4. (b) Martínez Palau, R. *Química en Microondas*; CEM Publishing: Matthews, NC, 2006; Chapter 3. (c) Kappe, C. O. *Angew. Chem., Int. Ed*. **2004**, *43*, 6250. (d) Lidstrom, P.; Tierney, J. P.; Wathey, B.; Westman, J. *Tetrahedron*, **2001**, *57*, 9225. (e) de la Hoz, A.; Díaz-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem*. **2000**, 3659.

(9) Solvent-free microwave-assisted cycloaddition did not give the desired results. The reactions performed at 300 W produced a very low yield of product due to decomposition of the reagent.

(10) The cycloaddition reaction of **1** and **3a** in THF at 200 W during 10 min affords the meta adduct as the unique product.