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Highly regioselective Diels–Alder reactions of 9-substituted anthracenes and 2-acetamidoacrylate: synthesis of conformationally constrained α-amino acids

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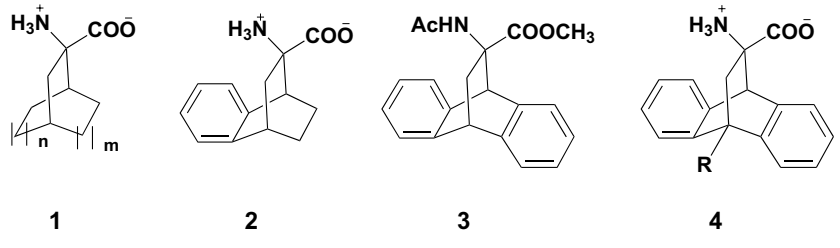
Abstract—The highly regioselective Diels–Alder reactions of 9-substituted anthracenes and 2-acetamidoacrylate afford a series of novel and conformationally constrained bicyclic bisaryl α-amino acids.

Conformationally constrained α-amino acids are valuable in biochemistry as modified peptides, enzyme inhibitors, and ligands for probing receptor recognition.[1] Consequently considerable efforts have been devoted to the de novo design of novel structures and methods for their synthesis. A recent approach employed Diels–Alder reactions of dehydroalanine derivatives to form the constrained bicyclic aliphatic α-amino acids **1** (Fig. 1).[2] The bicyclic monoaryl α-amino acids (e.g., **2**), rigid analogs of phenylalanine,[3] were prepared from the corresponding ketone via Bucherer–Bergs reaction, a non Diels–Alder route.[4] On the other hand, the highly constrained bicyclic bisaryl α-amino acids have received little attention. Only one approach has been reported for entry to the bicyclic bisaryl α-amino acid skeleton. Kotha et al. described the synthesis of **3** from the Diels–Alder reaction of 2-acetamidoacrylate and anthracene.[5a] However, this procedure using unsubstituted anthracene limited the adduct diversity in that it might not be widely applicable for substituted anthracenes. In particular, regioselectivity of the cycloadducts from Diels–Alder reaction of 9-substituted anthracenes and 2-acetamidoacrylate has not been investigated previously.[6] In this communication, we wish to report our studies on Diels–Alder reactions of 9-substituted anthracenes[7] with 2-acetamidoacrylate whereby a range of bicyclic bisaryl α-amino acids **4** are readily obtained with high regioselectivity.

Our first investigation into the Diels–Alder reaction of 2-acetamidoacrylate with 9-methylanthracene or 9-chloroanthracene in toluene employed the literature procedure,[5] that is, heating reaction in a sealed tube at 135 °C for 3 days (Scheme 1). However, these reactions



1 2 3 4

Figure 1.

Keywords: Regioselective; Diels–Alder reaction; 9-Substituted anthracenes; Conformationally constrained α-amino acids.
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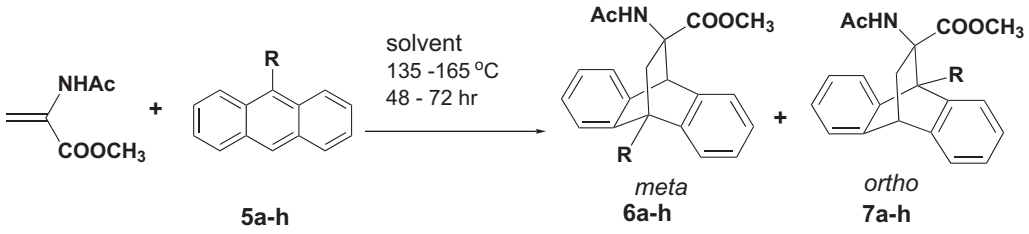


Scheme 1.

Table 1. Diels–Alder reactions of 9-substituted anthracenes and 2-acetamidoacrylate[a,b]

Entry	5	R	Solvent	*T* (°C)	Time (h)	6/7 *m*/*o*-Ratio[c]	%*meta* Yield[d]
1	**5a**	CH_3	Toluene	135	72	7/1	44[e]
2	**5a**	CH_3	$PhNO_2$	165	72	20/1	47
3	**5a**	CH_3	DMF	165	72	>99/1	(31)
4	**5b**	Cl	Toluene	135	72	—	0
5	**5b**	Cl	Toluene	165	48	4/1	19[e]
6	**5b**	Cl	$PhNO_2$	165	72	49/1	42
7	**5c**	NO_2	$PhNO_2$	165	48	>99/1	60
8	**5d**	Br	$PhNO_2$	165	72	27/1	25
9	**5e**	CH_2OAc	$PhNO_2$	165	72	>99/1	39
10	**5f**	CH_2OCH_3	$PhNO_2$	165	72	>99/1	39
11	**5g**	$COOCH_3$	$PhNO_2$	165	72	14/1	(25)[f]
12	**5h**	CN	$PhNO_2$	165	72	—	0

[a] General procedure: Anthracene (1 equiv), 2-acetamidoacrylate (2 equiv) and hydroquinone (0.1 equiv) in the specified solvent were placed in a sealed tube and were heated at the designated (oil bath) temperature and for the times indicated in the table.
[b] All isolated products are fully characterized by NMR, MS, and HPLC.
[c] The ratio of *meta* and *ortho* isomers 6/7 was determined by HPLC analysis of the crude reaction mixture. When there is no 'detectable' *ortho* isomer, the minimum *meta*/*ortho* ratio is at least >99/1 within the lowest limits of detection in HPLC.
[d] Isolated yield of *meta* isomer after flash chromatography, with no optimization. %Conversion of 9-substituted anthracenes, determined by HPLC analysis of the reaction mixtures, are in parentheses.
[e] Combined yield of a mixture of *meta* and *ortho* isomers after flash chromatography.
[f] The product characterized by HPLC and LCMS was identical to the authentic sample obtained from a microwave assisted reaction (vide infra).

were either not sufficiently regioselective or low yielding (Table 1, entries 1 and 4).

We next turned our attention to the reaction medium and temperature. When the oil bath temperature was raised to 165 °C, reaction with 9-chloroanthracene in toluene for 48 h generated adducts in 19% yield as a 4:1 mixture of *meta* and *ortho* isomers (entry 5). Polar solvents have been shown to increase the reaction rate for certain Diels–Alder reactions.[8] Nitrobenzene, an aprotic polar solvent, was selected because its high boiling point and low reactivity would allow reactions to be carried out under elevated temperatures for extended times. Additionally, the solubility of anthracenes in nitrobenzene was an added advantage. The results are summarized in Table 1.

To our delight, we found that using nitrobenzene, cycloaddition of 9-methylanthracene **5a** or 9-chloroanthracene **5b** (165 °C, 72 h) afforded the corresponding *meta* isomers **6a** or **6b** as the predominant products with *meta*/*ortho* ratios of 20/1 and 49/1, respectively (entries 2 and 6). More encouraging, 9-nitroanthracene **5c**, 9-acetoxymethylene **5e** and 9-methoxymethylene **5f** in nitrobenzene produced the *meta* adducts with no detectable *ortho* isomers[9] (entries 7, 9, and 10). All *meta* isomers were readily obtained in pure form using flash chromatography in moderate to good yields. The structural assignment of the regioisomers was determined by ^1H NMR analysis of the bridgehead protons. The bridgehead proton in the *meta* isomer is a singlet, whereas in the *ortho* isomer it is a triplet.[10]

The bulky bromoanthracene **5d** was found to produce a *meta*/*ortho* mixture of 27/1 in only 25% yield under the same conditions (entry 8). The methyl anthracene-9-carboxylate **5g** proceeded in about 25% conversion by HPLC (entry 11). Attempts to apply the above procedures to anthracene-9-carbonitrile **5h** resulted in no cycloadduct, presumably due to the effects of the strong electron-withdrawing cyano group (entry 12). It is worth mentioning that in DMF, reaction of **5a** generated the *meta* isomer **6a** with *meta*/*ortho* ratio >99/1 (entry 3), a substantial increase over that using nitrobenzene (*meta*/*ortho* 20/1, entry 2). However, the reaction yield was low (31% conversion).

Microwave assisted Diels–Alder reactions are gaining increased importance.[11] As an extension of the thermal reaction of 2-acetamidoacrylate and 9-substituted anthracenes, we decided to use microwave irradiation to determine the effects on the yield and regioselectivity of the Diels–Alder reaction. The results are summarized in Table 2.

Table 2. Microwave[a] assisted Diels–Alder reactions of 9-substituted anthracenes and 2-acetamidoacrylate (200 °C, 1 h)[b]

Entry	5	R	Solvent	Acrylate (equiv)	6/7 *m*/*o*-Ratio[c]	%Conversion of 5[c]	%*meta* Yield[d]
1	**5a**	CH_3	$PhNO_2$	2	19/1	35	
2	**5a**	CH_3	DMF	2	20/1	42	
3	**5b**	Cl	DMF	2	30/1	33	
4	**5c**	NO_2	DMF	2	50/1	19	
5	**5d**	Br	DMF	2	>99/1	20	
6	**5d**	Br	DMF	5	>99/1	43	40
7	**5e**	CH_2OAc	DMF	5	>99/1	48	45
8	**5f**	CH_2OCH_3	DMF	5	>99/1	50	48
9	**5g**	$COOCH_3$	DMF	5	35/1	25	19
10	**5h**	CN	DMF	5	nd	<1[e]	

nd: not determined.

[a] Reactions were run in the Emry™ process vials under microwave irradiation using the Smith Synthesizer™ from Personal Chemistry.

[b] Reactions run at the scale of 100 mg of 9-substituted anthracene with a molar ratio of 1:2:0.1 or 1:5:0.1 for anthracene/2-acetamidoacrylate/hydroquinone at 200 °C for 1 h.

[c] The reaction mixtures were directly assayed by HPLC for the ratio of *meta* and *ortho* isomers **6/7** and %conversion of the 9-substitued anthracenes.

[d] Isolated yields of *meta* isomer after flash chromatography, with no optimization.

[e] Product was characterized by HPLC and LCMS without isolation.

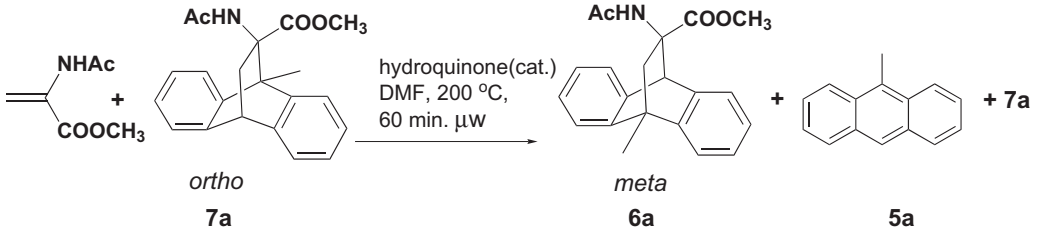
The best results were achieved in DMF, a polar and high-absorbing (microwave energy) solvent.[11d,e] Reaction of **5a** at 200 °C for 1 h resulted in 42% conversion with a good *meta* regioselectivity (*meta*/*ortho* 20/1, entry 2) similar to the results using conventional heating in nitrobenzene (Table 1, entry 2). In this case, nitrobenzene was not the optimal solvent under the microwave irradiation (entry 1). 9-Bromoanthracene **5d** in DMF afforded the *meta* isomer **6d** exclusively (entry 5). When 5 equiv of 2-acetamidoacrylate were employed, reactions of **5d**,**e**, and **5f** in DMF attained *meta* isomers **6d**,**e**, and **6f** in 40%, 45%, and 48% yields, respectively (entries 6–8). Under the same conditions, reaction of methyl anthracene-9-carboxylate **5g** gave the *meta* isomer **6g** in 19% yield with a *meta*/*ortho* ratio of 35/1 (entry 9).

As demonstrated by the results in Table 2, compared to thermal conditions, microwave irradiation offers the advantage of significant increases in reaction rate. In addition, employment of an excess of the dienophiles accompanied by a decrease of side reactions under microwave heating and the facile purification of the reaction mixture in DMF resulted in increased reaction yields in most cases.

We observed that under both conventional heating and microwave irradiation conditions, the formation of the *ortho* isomer was suppressed at elevated temperatures. This is probably due to retro Diels–Alder reaction of the initially formed *ortho* isomer which is thermodynamically less stable than the *meta* isomer. To test the possibility of a retro Diels–Alder reaction mechanism, we investigated the reaction of *ortho* isomer **7a** with 5 equiv of 2-acetamidoacrylate in the presence of a catalytic amount of hydroquinone (Scheme 2). When exposed to microwave irradiation in DMF at 200 °C for 60 min, the reaction produced a product mixture containing 10% of the *meta* isomer **6a** and 89.2% 9-methylanthracene **5a** with 0.8% of the *ortho* isomer **7a** (HPLC analysis). Evidently, the *ortho* isomer **7a** undergoes a retro Diels–Alder reaction that generates the 9-methylanthracene eventually leading to the formation of the thermodynamically more stable *meta* isomer **6a**.

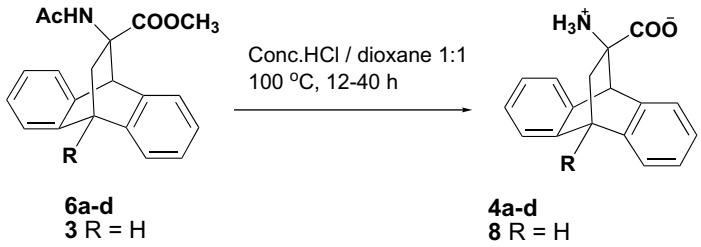
Finally, hydrolysis of the Diels–Alder adduct esters **6a**–**d** and **3** in HCl–dioxane furnished the corresponding bicyclic bisaryl α-amino acids **4a**–**d** and **8** uneventfully (Table 3).

In summary, we have developed a facile preparation of a series of novel and conformationally constrained bicyclic bisaryl α-amino acids with high regioselectivity via Diels–Alder reactions of 9-substituted anthracenes and 2-acetamidoacrylate. Suppression of *ortho* isomer's formation via retro Diels–Alder reaction followed by regeneration of the *meta* isomer resulted in the high *meta* regioselectivity. Use of nitrobenzene in a thermal Diels–Alder reaction or DMF under microwave irradiation at elevated temperatures was shown to enhance the *meta* regioselectivity and improve reaction yields. Further studies on the scope and regioselectivity of the Diels–Alder reactions of substituted anthracenes with



Scheme 2.

Table 3. Hydrolysis of Diels–Alder reaction adduct **6**



6a-d
3 R = H

4a-d
8 R = H

Entry	Ester	R	Time (h)	Acid	% Yield[a]
1	**6a**	CH_3	18	**4a**	89
2	**6b**	Cl	16	**4b**	99
3	**6c**	NO_2	40	**4c**	91
4	**6d**	Br	12	**4d**	89
5	**3**[b]	H	12	**8**	90

[a] Yields of isolated products with no optimization.
[b] Compound **3** was prepared from the Diels–Alder reaction of 2-acetamidoacrylate and anthracene in 60% yield employing the procedure described in Table 1 entry 2.

a variety of dienophiles under microwave irradiation are in progress.

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9. At the lowest limits of detection in HPLC the minimum *meta*/*ortho* ratio is at least >99 to 1 (absence of the *ortho* isomer confirmed by ^{1}H NMR as well).
10. Analytical data for representative compounds, *meta* isomer **6a** and *ortho* isomer **7a** (Table 1, entry 1): **6a** ^{1}H NMR (500 MHz, MeOH-d_4) δ 7.34 (t, J = 8 Hz, 2H), 7.25 (m, 3H), 7.17 (m, 2H), 7.09 (td, J = 8, 1.3 Hz, 1H), 5.64 (br s, 1H), 4.44 (s, 1H), 3.48 (s, 3H), 2.89 (d, J = 13.6 Hz, 1H), 1.93 (s, 3H), 1.78 (s, 3H), 1.53 (d, J = 13.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.2, 169.5, 146.3, 145.2, 138.8, 138.4, 127.2, 126.8, 125.9, 125.7, 124.9, 124.7, 121.4, 120.9, 63.8, 52.5, 52.2, 47.4, 42.6, 22.8, 17.1; MS (ESI): *m*/*z* 336.29 $[M+H]^+$. **7a** ^{1}H NMR (400 MHz, MeOH-d_4) δ 7.50 (dd, J = 8, 1.6 Hz, 1H), 7.32 (td, J = 8, 1.6 Hz, 2H), 7.21 (m, 3H), 7.15 (m, 2H), 4.34 (t, J = 2.6 Hz, 1H), 3.38 (s, 3H), 3.06 (dd, J = 13.3, 2.6 Hz, 1H), 2.02 (s, 3H), 1.85 (dd, J = 13.3, 2.6 Hz, 1H), 1.84 (s, 3H); MS (ESI): *m*/*z* 336.29 $[M+H]^+$.
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