Pergamon

Bioorganic & Medicinal Chemistry Letters 10 (2000) 1755–1757

BIOORGANIC & MEDICINAL CHEMISTRY LETTERS

Diels–Alder Approach to Tetralin-Based Constrained α-Amino Acid Derivatives†

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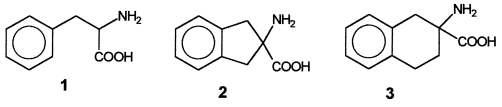
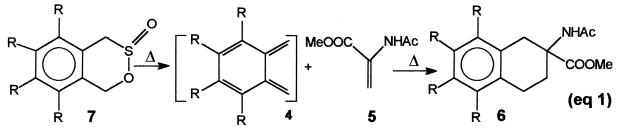
Received 5 April 2000; accepted 6 June 2000

Abstract—Tetralin-based constrained α-amino acid derivatives were prepared via [4 + 2]-cycloaddition reaction as a key step. Here sultine is used as a latent diene and 2-acetamidoacrylate serves as a dienophile component.

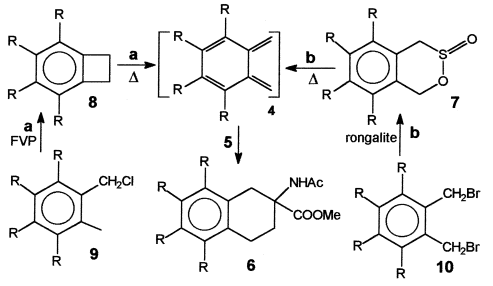
Traditional peptide structure–activity studies employing proteinogenic amino acids have a limited potential. Many exciting possibilities are opened up when such studies involve the incorporation of nonproteinogenic amino acids with sterically demanding side-chains. For example, a large variety of structural variations are feasible even with tri or tetra-peptide by single amino acid replacements.[1] The realisation of these goals are aided by the development of new and general synthetic methods[2] that can deliver nonproteinogenic (or unusua1) α-amino acids (AAAs) with varying degree of topographical,[3] steric and electronic properties. On several occasions, when phenylalanine **1** is replaced with 2-indanyl glycine **2** in peptide modifications, the resulting peptidomemitics had shown enhanced desirable properties.[4] In this regard, we had demonstrated several new and novel methodologies for various derivatives of **2**.[5]



As part of our program directed towards the synthesis of constrained AAA derivatives via building block approach, we conceived a new strategy to 2-aminotetralin-2-carboxylic acid derivatives of **3** using Diels–Alder reaction as a key step. The literature synthesis of **3**[6] involves Bucherer–Berg (BB) method[7] starting from the commercially available 2-tetralone. Unfortunately, BB methodology requires drastic reaction conditions for the hydrolysis of the intermediate spirohydantoin and consequently many sensitive substrates are not suitable for this purpose.[8] In this communication, we would like to report our preliminary results towards the synthesis of tetralin-based AAA derivatives by trapping various transient *o*-xylylene intermediates[9] (e.g., **4**) with 2-acetamidoacrylate **5**[10] in a Diels–Alder fashion (eq 1). The retrosynthetic strategy for tetralin-based AAA derivatives related to **6** is shown in Scheme 1. Path **a** involves the thermal isomierization of the benzocyclobutene (BCB) **8** to *o*-xylylene **4** followed by its Diels–Alder reaction with **5**. The second route (path **b**) rely on chelotropic elimination of sulfur dioxide from sultine **7** leading to the formation of transient intermediate **4** which in turn reacts with **5** to generate AAA derivative **6**. Although both these routes involve the same intermediate, the method of generation of **4** is crucial in the present context. Several other reductive elimination methods for the generation of **4** which are incompatible with **5** are not considered here.[9]



Towards the synthesis of compounds of type **6**, initially BCB was reacted with **5**[10] at various temperatures (80–



Scheme 1.

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†This paper is dedicated to Prof. G. K. Trivedi on the occasion of his 60th birthday.

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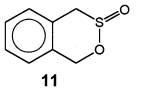
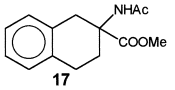
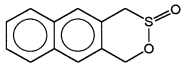
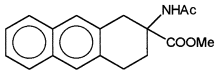
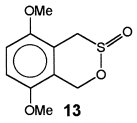
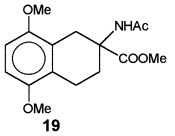
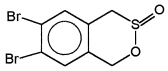
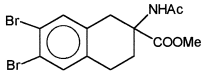
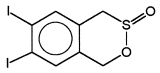
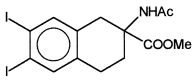
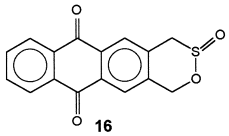
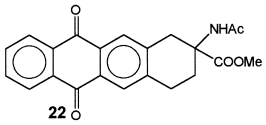
Table 1.

S. no.	Sultine structure	Yield	Diels–Alder product	Yield/conditions
1	 **11**	83%	 **17**	66% benzene reflux 20 h
2	 **12**	34%	 **18**	63% toluene reflux 40 h
3	 **13**	57%	 **19**	64% toluene sealed tube/130 °C 48 h
4	 **14**	35%	 **20**	35% xylene 80 °C 42 h
5	 **15**	60%	 **21**	91% toluene sealed tube/130 °C 72 h
6	 **16**	20%	 **22**	40% xylene 110 °C 34 h

120 °C) and found that no Diels–Alder product was observed. Since the parent BCB undergoes thermal cyclobutene ring opening at 200 °C,[11] BCB (**8**, R=H) and **5** was reacted in xylene in a sealed tube at 180–200 °C and found several products as indicated by TLC analysis. At this juncture it occurred to us that a milder method for the generation of *o*-xylylene such as **4** is desirable in the present case. Moreover, generation of **4** in the absence of dienophile is known to undergo dimerization and/or polymerization to generate unwanted products. A perusal of literature indicated that generation of *o*-xylylene such as **4** by thermal elimination of sulfur dioxide from sultine, l,4-diliydro-2,3-benzoxathiin-3-oxide **7** requires lower temperature than the other benzo-fused cyclic precursors. Accordingly, to test our idea, the parent sultine[12] was prepared and reacted with **5** at benzene reflux temperature gave the required product in 66% isolated yield.

Having established the conditions for trapping *o*-xylylene in the presence of **5**, next we turned our attention to expand this strategy to other related substrates. Various tetralin-based AAA prepared in this regard are outlined in Table 1. All these compounds are identified by their complementary spectral data.[13]

In conclusion, we have shown that various *o*-xylylene derivatives derived from sultines are trapped with 2-acetamidoacrylate **5** in a Diels–Alder fashion to generate various tetralin-based constrained AAA derivatives. It is worth mentioning that compounds of type **22** are inaccessible by the currently available methods due to the presence of keto functionality. Moreover, the starting keto precursors sensors for BB method is not a trivial exercise. Since constrained AAA derivatives play an important role in the design of biologically active peptides, our results may be of interest to medicinal and bioorganic chemists working in these areas.

Acknowledgements

We thank DST for financial support and RSIC-Mumbai for recording the spectral data.

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12. Hoey, M. D.; Dittmer, D. C. *J. Org. Chem.* **1991**, *56*, 1947.
13. In a typical experimental procedure a solution of suitine and 2-acetamidoacrylate in benzene or toluene was refluxed until the starting materials had disappeared. At the conclusion of the reaction (TLC), the solvent was removed at reduced pressure and the crude product was purified by silica gel column chromatography. Elution of the column with ethyl acetate–hexane mixture gave the required product. Selected 13 NMR data: (**17**, $CDCl_3$), δ 23.0, 25.1, 27.7, 37.8, 52.5, 57.7, 126.1, 126.5, 128.8, 129.5, 131.9, 134.9, 170.1, 173.9. (**18**, $CDCl_3$), δ 23.0, 25.4, 28.6, 38.3, 52.6, 58.1, 125.4, 125.7, 126.8, 127.0 (2C ?), 127.7, 130.9, 132.1, 132.5, 133.4, 170.1, 173.9. (**19**, $CDCl_3$), δ 19.6, 23.0, 26.2, 32.6, 52.5, 55.5 (2C ?), 56.9, 107.0, 107.3, 122.0, 125.5, 151.0, 151.5, 169.9, 174.2. (**20**, DMSO-d_6), δ 22.2, 24.0, 27.8, 35.7, 52.0, 56.3, 120.4, 120.5, 133.1, 133.8, 135.6, 136.7, 169.6, 173.5. (**21**, DMSO-d_6), δ 22.2, 23.8, 27.7, 35.6, 51.9, 56.3, 104.6, 104.8, 135.9, 137.1, 138.6, 139.3, 169.6, 173.5.