Synthesis of dibenzocyclobutenylglycine derivatives

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Dedicated to Prof. S. V. Kessar on the occasion of his 70th birthday

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Abstract

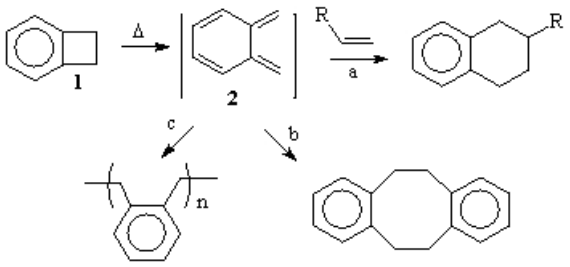
Several dibenzocyclobutenylglycine derivatives **9**-**12** have been prepared by dialkylation of ethyl isocyanoacetate **8** under NaH/DMSO reaction conditions.

Keywords: Amino acids, benzocyclobutene, alkylation

Introduction

Benzocyclobutene (BCB) **1** and its derivatives represent a unique class of reactive molecules because of the thermodynamic stability associated with the aromatic system and the kinetic reactivity of the strained cyclobutene ring. BCB undergoes three types of reactions under thermal activation. For example, BCB readily isomerise to *o*-xylylene **2**, which can be trapped with various dienophiles in inter- and intramolecular fashion to generate various polycyclic systems (path a, Scheme 1). *o*-Xylylene intermediates in the absence of dienophiles dimerise or polymerise. The dimerisation process has been employed for the preparation of cyclophanes from suitably substituted benzocyclobutene precursors (path b). Alternatively, polymerisation (path c) constitutes an important route for the synthesis of high performance polymers for applications in the electronics and aerospace industries. The fate of *o*-xylylene in the absence of other co-reactive species appears to depend to a large extent upon the conditions under which it is generated.

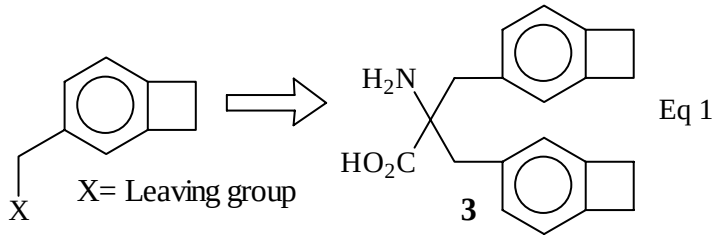
A range of dienophilic partners engage BCBs via their *o*-xylylene intermediates in [4+2] cycloadditions.[1] Over the years, BCBs have emerged as versatile chemical entities and their syntheses and chemical reactivity continue to draw the attention of organic chemists. More recently, BCBs have served as important building blocks for natural product syntheses and for new polymers and advanced materials.[2]



Scheme 1

Strategy

With reference to our interest in the synthesis of several dibenzylglycine derivatives[3] under PTC conditions[4] and also functionalization of BCB by Suzuki-Miyaura coupling reaction[5] we thought that dialkylation of ethyl isocyanoacetate with suitably substituted BCB may be a useful strategy for the preparation of **3** (Eq 1). In view of varied applications of BCB in organic synthesis and polymer synthesis it occurred to us that amino acids containing BCB unit (eg **3**) might provide an unique opportunity for post-translational peptide modifications[6] *via* the Diels-Alder methodology.

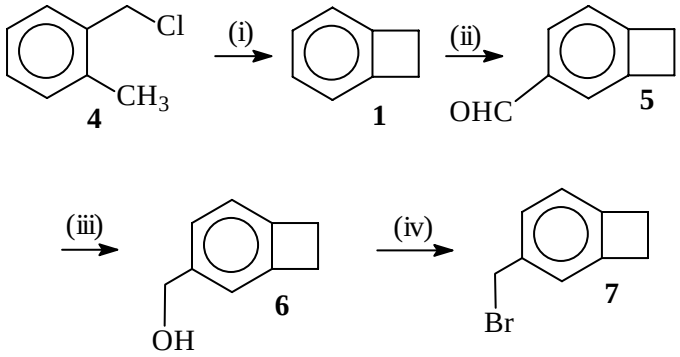


Results and Discussion

Towards the synthesis of amino acid derivatives **3**, the required bromo derivative **7** was prepared in a four-step sequence starting from α-chloro-*o*-xylene **4** as shown in Scheme 2. Thus, flash vacuum pyrolysis of α-chloro-*o*-xylene **4** at 780 ^{0}C (0.3 mm/Hg) gave the crude benzocyclobutene along with the unreacted starting material **4**. The crude reaction mixture was treated with excess amount of powdered KOH in presence of DMSO to remove the starting material as reported in the literature gave the pure BCB **1.**[7] Formylation of **1** with Cl_2CHOMe in presence of $TiCl_4$ [8] in dry dichloromethane at 0 ^{o}C gave the required aldehyde **5** in 34% yield.

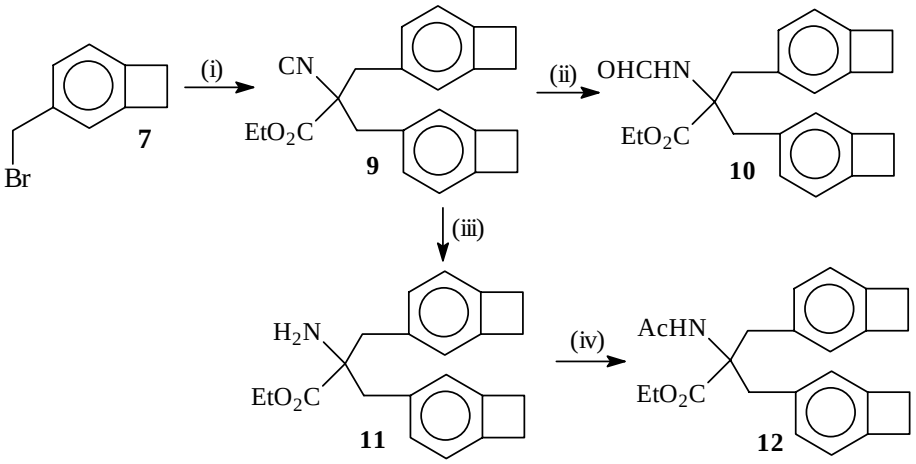
Then, the aldehyde **5** was reduced to hydroxy derivative **6** by treatment with $NaBH_4$ in dry methanol at 0 ^{o}C gave 85% yield (mp 59-60 ^{o}C). The hydroxy derivative was prepared in the literature from a suitably protected mono alkyne by a [2+2+2] cycloaddition reaction.[9]

Conversion of hydroxy compound **6** to the corresponding bromo derivative **7** proved to be more difficult than anticipated. Initial attempts to prepare the bromo derivative **7** under PBr_3/diethyl ether/pyridine conditions gave the ring-opened product along with minor amount of required bromo derivative **7**. Later on, attempts to prepare the tosyl derivative from **6** under various reaction conditions were unsuccessful.



Scheme 2. (i) FVP, 780 ^{o}C/0.3Hg mm (ii) TiCl 4, Cl_2CHOCH_3 (iii) $NaBH_4$, MeOH (iv) Nabr, BF_3OEt_2, CH_3CN.

After considerable amount of experimentation we found that treatment of **6** with $NaBr/BF_3OEt_2$[10] in acetonitrile at 0 ^{o}C gave the required bromo derivative **7** in 70% isolated yield which was characterized on the basis of complementary spectral data. The ^{1}H NMR spectrum of **7** showed diagnostic two singlets at δ 3.15 and 4.50 due to cyclobutene ring protons and benzylic protons respectively. The 9-line ^{13}C NMR spectrum [δ 29.3, 29.4, 35.0, 122.8, 123.2, 127.8, 136.4, 146.3] established the structure of **7**.



Scheme 3. (i) $CNCH_2CO_2Et$ (**8**), NaH/DMSO, 0 ^{o}C (ii) H^+, diethyl ether, 0 ^{o}C (iii) H^+, EtOH (iv) Ac_2O, dichloromethane.

Towards the synthesis of amino acid derivative such as **3**, bromo derivative **7** was treated with ethyl isocyanoacetate **8** under NaH/DMSO conditions at 0 ^{o}C to give the dialkylated product **9** (Scheme 3). The structure of compound **9** was in full agreement with the spectral data. The IR absorption at 2137 and 1731 cm^{-1} describe the presence of isonitrile and ester functionalities respectively. The 14-line ^{13}C NMR spectrum [δ 13.9, 29.3, 29.4, 45.5, 62.3, 70.6, 122.4, 124.5, 129.0, 132.0, 145.2, 145.7, 161.4, 168.1] further supported the presence of C_2 symmetry in the molecule **9**.

The isonitrile derivative **9** was hydrolyzed in presence of diethyl ether/HCl at RT to deliver the formyl derivative **10**. The structure of **10** has been established by complementary spectral data. The absence of strong absorption band in the IR spectrum at 2137 cm^{-1} due to isonitrile group and the presence of broad absorption band at 3381 cm^{-1} due to amino group and also two sharp absorption bands at 1735 and 1671 cm^{-1} due to ester and formyl groups respectively, revealed the formation of compound **10**. The isonitrile derivative was also hydrolyzed in presence of HCl/EtOH to give the amino ester derivative **11.** The amino group of **11** was then protected by acetylation with acetic anhydride in dry dichloromethane at RT to give **12**. The ^{1}H NMR spectrum of **12** showed a triplet at δ 1.41 (t, *J* =7.1 Hz) and a quartet at δ 4.22 (q, *J* =7.1 Hz) due to ethyl ester functionality, a part of ½ ABq at δ 3.17 (*J* =13.5 Hz) and other part of ½ ABq at δ 3.96 (*J* =13.5 Hz) due to diastereotopic protons. The two singlets at δ 1.95 and 3.10 due to acetyl and cyclobutene ring protons respectively.

Conclusions

We have shown that NaBr/BF_3OEt_2 protocol is useful for ROH to RBr transformation where cyclobutene ring system is involved. For the first time, we have prepared dialkylated BCB-based α-amino acid (AAA) derivatives using ethyl isocyanoacetate as a glycine equivalent in good yield. Since amino acid derivatives with unusual side chains have many applications in organic synthesis and peptide modifications, our results may find useful applications in bioorganic and medicinal chemistry.

Experimental Section

General Procedures. Flash vacuum pyrolysis was carried out with home made quartz pyrolysis equipment. BF_3OEt_2 and DMSO were dried over CaH_2 and then distilled at reduced pressure under inert atmosphere. Dry diethyl ether was obtained by distillation over benzophenone ketyl. α-chloro-*o*-xylene and ethyl isocyanoacetate were purchased from Aldrich Chemical Co.

Synthesis of 3-hydroxymethyl benzocyclobutene (6).[9] To a stirred solution of aldehyde **5** (1.1 g, 8.3 mmol) in dry methanol (30 mL) was added sodium borohydride (314 mg, 8.3 mmol)

in small portions at 0 ^{o}C and the reaction mixture was stirred at RT for 12 h. Then, the reaction mixture was quenched with water (2 mL) and extracted with ethyl acetate (25 mL × 3), combined organic layers were washed with water (15 mL), brine (15 mL) and dried over $MgSO_4$ evaporation of the solvent gave crude material which was purified by silica gel flash column chromatography. Elution of the column with 5% ethyl acetate/petroleum ether mixture gave **6** (950 mg, 85%) as a white solid. Mp: 59-60 ^{o}C (Lit mp 45 ^{o}C).[6] IR (KBr): ν 3351 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.63 (br s, 1H), 3.17 (s, 4H), 4.63 (s, 2H), 7.02-7.20 (m, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 29.4, 66.0, 121.6, 122.5, 125.9, 139.6, 145.3, 146.1. Mass: m/z 134 (M^+).

Synthesis of 3-bromomethyl benzocyclobutene (7). To a solution of alcohol **6** (200 mg, 1.49 mmol), sodium bromide (228 mg, 2.21 mmol) in dry acetonitrile (15 mL) was added BF_3OEt_2 (312 mg, 2.21 mmol) at 0 ^{o}C. Then, the reaction mixture was brought to RT slowly and stirred for 8 h. The solution was cooled at 0 ^{o}C and quenched with saturated $NaHCO_3$ solution and extracted with diethyl ether (30 mL × 3), combined organic layers were washed with water (20 mL), brine (15 mL) and dried over $MgSO_4$. Evaporation of the solvent gave the crude product which was purified by silica gel flash column chromatography. Elution of the column with petroleum ether gave **7** (205 mg, 70%) as a low melting solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.15 (s, 4H), 4.50 (s, 2H), 7.00-7.25 (m, 3H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 29.3, 29.4, 35.0, 122.8, 123.2, 127.8, 136.4, 146.3 (2C?). Mass: m/z 198 (M+1).

Ethyl 3-bicyclo[4.2.0]octa-1,3,5-trien-3-yl-2-bicyclo[4.2.0]octa-1,3,5-trien-3-ylmethyl-2-isocyano-propionate (9). To a stirred solution of bromo derivative 7 (50 mg, 0.25 mmol), ethyl isocyanoacetate (8) (17 mg, 0.15 mmol), DMSO (0.2 mL, 2.8 mmol) in dry diethyl ether (5 mL) was slowly added a slury of 60% NaH (13 mg, 0.32 mmol) in dry diethyl ether (4 mL) via a syringe at 0 ^{o}C. The reaction mixture was stirred at RT for 12 h and then quenched with water (2 mL) and extracted with diethyl ether (25 mL × 3). Combined organic layers were washed with water (20 mL), brine (15 mL) and dried over $MgSO_4$. Evaporation of solvent gave the crude product, which was purified by silica gel flash column chromatography. Elution of the column with 4% ethyl acetate/petroleum ether mixture gave dialkylated product 9 (32 mg, 73%) as a colorless liquid. IR (neat): ν 2137, 1731 cm^{-1}. UV ($CHCl_3$): λ nm (ε $M^{-1}cm^{-1}$) 277.0 (3.66×10^3), 270.5 (3.89×10^3). Mass: m/z 345 (M^+). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (t, J=7.1 Hz, 3H), 2.99 (1/2 ABq, J=13.5 Hz, 2H), 3.14 (s, 8H), 3.31 (1/2 ABq, J=13.5 Hz, 2H), 4.08 (q, J=7.1 Hz, 2H), 6.96-7.08 (m, 6H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 13.9, 29.3, 29.4, 45.5, 62.3, 70.6, 122.4, 124.5, 129.0, 132.0, 145.2, 145.7, 161.4, 168.1. HRMS: m/z (EI) for $C_{23}H_{23}NO_2$; calcd. 345.17288; found 345.17294.

Ethyl 3-bicyclo[4.2.0]octa-1,3,5-trien-3-yl-2-bicyclo[4.2.0]octa-1,3,5-trien-3-ylmethyl-2 formylamino-propionate (10). To a solution of the coupling product **9** (24 mg, 6.95 mmol) in diethyl ether (6 mL) was added concd HCl (3 drops) at 0 ^{o}C and stirred at RT for 12 h. The reaction mixture was diluted with diethyl ether (50 mL), and washed with water (20 mL), brine (20mL) and dried over $MgSO_4$. Evaporation of solvent gave the crude product, which was purified by silica gel flash column chromatography. Elution of the column with 7% ethyl acetate/petroleum ether mixture gave **10** (24 mg, 95%) as a white solid. mp 129-130 ^{o}C.

UV ($CHCl_3$): λ_{max} nm (ε $M^{-1}cm^{-1}$) 277.5 (4.27×10^3), 271.0 (4.61×10^3). IR (KBr): ν 3381, 1736, 1671 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, J=7.3 Hz, 3H), 3.10 (s, 8H), 3.25 (1/2 ABq, *J* =13.9 Hz, 2H), 3.89 (1/2 ABq, *J* =13.9 Hz, 2H), 4.23 (q, *J* =7.3 Hz, 2H), 6.20 (s, 1H), 6.79 (s, 2H), 6.92 (d, *J* =0.73 Hz, 4H), 8.18 (s, 1H). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ 14.3, 29.3, 29.4, 41.7, 61.9, 67.9, 122.3, 123.9, 128.3, 134.4, 144.3, 145.5, 160.5, 172.0. HRMS: m/z (EI) for $C_{23}H_{25}NO_3$; Calcd. 363.18344; found 363.18290.

Hydrolysis of 10. To a stirred solution of dialkylated derivative **9** (100 mg, 0.29 mmol) in absolute ethanol (5 mL) was added concd HCl (5 drops) at 0 ^oC and stirred at RT for 1h. The reaction mixture was concentrated under reduced pressure and diluted with water, washed with diethyl ether (20 mL) to remove unwanted organic residues. The aqueous layer was basified with ammonia solution to pH~10 and extracted with ethyl acetate (20 mL × 3), combined organic layers were washed with water (15 mL), brine (15 mL) and dried over $MgSO_4$. Evaporation of the solvent gave amino ester **11** (92 mg, 95%) which was directly used in the next step for acetylation reaction.

Ethyl 2-acetylamino-3-bicyclo[4.2.0]octa-1,3,5-trien-3-yl-2-bicyclo[4.2.0]octa-1,3,5-trien-3-ylmethyl-propionate (12). To a stirred solution of amino ester **11** (85 mg, 0.25 mmol) in dry dichloromethane (4 mL) was added acetic anhydride (51 mg, 0.5 mmol) and stirred at RT for 2 h. Then, the solvent was removed and extracted with ethyl acetate (25 mL × 3). The combined organic layers were washed with water (20 mL), brine (20 mL) and dried over $MgSO_4$. Evaporation of the solvent gave the crude product, which was purified by silica gel flash column chromatography. Elution of the column with 15% ethyl acetate/petroleum ether mixture gave acetylated product **12** (61 mg, 64%) as a sticky solid. IR (neat): ν 3407, 1743, 1676 cm^{-1}. UV ($CHCl_3$): λ_{max} nm (ε $M^{-1}cm^{-1}$) 270.5 (3.35×10^3), 276.5 (3.08×10^3). ^1H NMR (300 MHz, $CDCl_3$): δ 1.41 (t, *J* =7.1 Hz, 3H), 1.95 (s, 3H), 3.10 (s, 8H), 3.17 (1/2 ABq, *J* =13.5 Hz, 2H), 3.96 (1/2 ABq, *J* =13.5 Hz, 2H), 4.22 (q, *J* =7.1 Hz, 2H), 6.10 (s, 1H), 6.90-6.99 (m, 6H). Mass: m/z 377 (M^+). HRMS: *m/z* (EI) for $C_{24}H_{27}NO_3$; Calcd. 377.19909; found 377.19882.

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