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First and Unexpected Synthesis of Macrocyclic Cyclophane-Based Unusual α-Amino Acid Derivatives by Phosphazene Base without High Dilution Conditions

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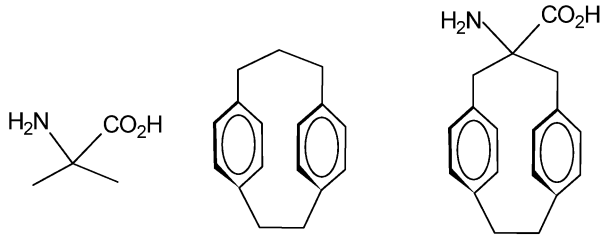
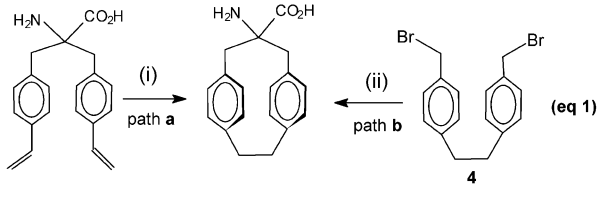
Abstract—First synthesis of a macrocylic cyclophane-based unusual α-amino acid derivative 11 by coupling of ethyl isocyanoacetate with 1,2-bis(4-bromomethylphenyl)ethane under phase-transfer catalysis (PTC) conditions. Phosphazene base such as 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) is useful to improve the yield of cyclophane derivative without high dilution conditions.

Aib (α-aminoisobutyric acid) **1** is an important structural motif in the design and synthesis of several well-defined and biologically important peptide drugs.[1] In this regard, several other structural variants of Aib were introduced in numerous peptides to control/understand the structure reactivity pattern.[2] So, we are interested in preparing an unusual α-amino acid (AAA) derivative **3** which is a hybrid of Aib **1** and [3,2]paracylophane unit **2**. Availability of such AAA can act as a useful model compound for the study of transannular electronic effects in a polypeptide chain. Moreover, such AAA derivatives are expected to affect the topology and lipophilicity of the peptide chain into which they are incorporated. In addition, cyclophanes represent the central class of synthetic receptors in molecular recognition.[3a] To the best of our knowledge, no reports are available for the synthesis of AAA containing cyclophane unit as a side chain.



1 **2** **3**

Motivated by these issues, two approaches for the synthesis of AAA with cyclophane unit as a side chain (eq 1) were conceived. Path **a** (eq 1) involves ring-closing metathesis (RCM) reaction as a key step. Path **b** consists the coupling of 1,2-bis(4-bromomethylphenyl)ethane **4** with a suitable glycine equivalent.



(i) RCM, H_2 / Pd-C (ii) Glycine equivalent. (eq 1)

(1)

To realize the first strategy (path **a**), ethyl isocyanoacetate was reacted with 4-vinylbenzyl chloride **5** in presence of NaH/DMSO to give dialkylated product **6** in 90% yield (Scheme 1). The alkylated product **6** was characterized on the basis of ^{13}C NMR and mass spectral data. 12-Line ^{13}C NMR (δ 13.8, 44.5, 62.6, 70.1, 114.1, 126.2, 130.4, 133.0, 136.3, 137.1 161.2, 167.8) and

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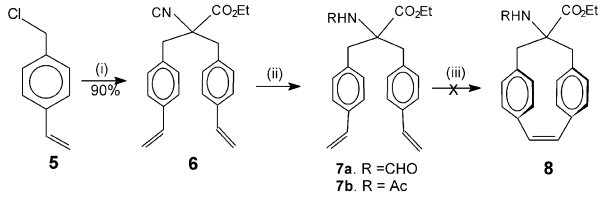
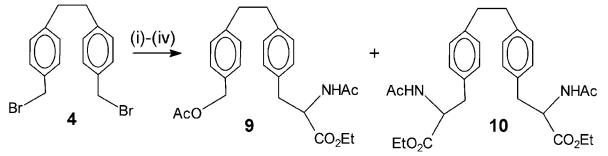


Scheme 1. (i) $CNCH_2CO_2Et$, NaH, DMSO, ether, rt; (ii) H^+, ether or H^+, EtOH, Ac_2O; (iii) Grubbs' catalyst.

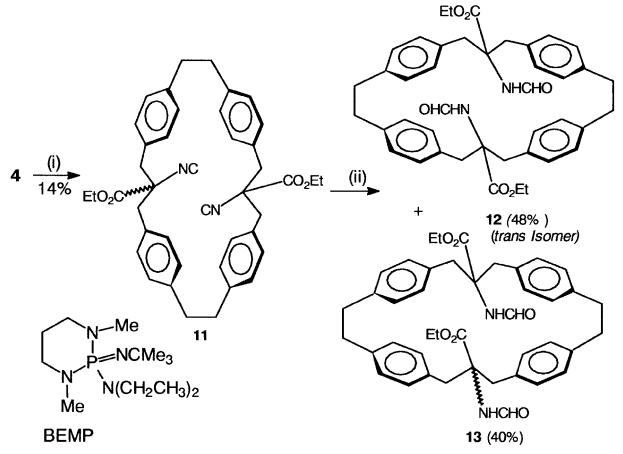
mass ($m/z = 345$) spectral data supported its formulation. The isonitrile derivative **6** was hydrolyzed with HCl/ether to give *N*-formyl derivative **7a**. The disappearance of peak at 2137 cm^{-1} and appearance of peak at 1667 cm^{-1} in the IR spectrum indicate the presence of N–CHO group; in ^1H NMR (300 MHz) spectrum signal at δ 8.18 due to aldehyde proton supports the formation of *N*-formyl derivative **7a**. When the RCM reaction[3b] was carried out with the compound **7a** in presence of Grubbs' catalyst [bis(tricyclohexyl-phosphine)benzylidine ruthenium(IV) dichloride] in either degased refluxing benzene or in dichloromethane under argon atmosphere, the required cyclophane derivative **8** was not formed and the unreacted starting material was recovered. Alternatively, *N*-acetyl derivative **7b** was also prepared and found to be inert to RCM reaction under similar reaction conditions.

Then, the alternate strategy (path **b**), involving alkylation of *N*-(diphenylmethylene)glycine ethyl ester (Schiff-base) with dibromide **4** was attempted. The required dibromide **4** was prepared by bromomethylation of 1,2-diphenylethane according to the known procedure.[4a] Alkylation of Schiff-base[4b] with **4** in presence of KOH/TBAB (tetra-*n*-butylammonium bromide) in acetonitrile at 0 °C followed by hydrolysis and protection with acetic anhydride gave *N*-acetyl derivatives **9** (8%) and **10** (7%) (Scheme 2). Compounds **9** and **10** were isolated by silica gel column chromatography[5] and were characterized by ^1H NMR and mass spectral data. 12-Line ^{13}C NMR spectral data (δ 14.2, 23.2, 37.5, 37.6, 53.2, 61.5, 128.6, 129.3, 133.5, 140.5, 169.6, 171.7) also supported the presence of C_2 symmetry in the molecule **10**. Since the phase transfer catalysis (PTC) conditions did not deliver the coupling product related to **3**, alkylation in presence of micelle, cetyltrimethyl-ammonium bromide (CTAB) was attempted where the favorable entropy conditions may aid the formation of the required cyclophane derivative.[6] Surprisingly, under these conditions, reaction of **4** with Schiff-base followed by hydrolysis and acetylation gave **9** (6%) and **10** (13%).[5]



Scheme 2. (i) Schiff-base; (ii) KOH, TBAB or Micelle (CTAB), CH_3CN; (iii) H^+, ether, rt; (iv) Ac_2O, DMAP, CH_2Cl_2, rt.

At this juncture, the change of glycine equivalent from Schiff-base to ethyl isocyanoacetate was considered. When the dibromide **4** was treated with ethyl isocyanoacetate under PTC conditions,[7a] the alkylated product **11** (mp 190–192 °C) was isolated in 3.5% yield (Scheme 3). Compound **11** was characterized on the basis of ^1H NMR and mass spectral data. ^{13}C NMR spectral data shows the mixture of two isomers in 5:6 ratio, which were separated after hydrolysis. It is known in the literature that the bromide **4** can form radical intermediates under thermal or photochemical reaction conditions to give disproportion/polymerization reaction,[7b] and the low coupling yield of the product can be explained due to this possible unwanted side reaction. To test this idea, alkylation reaction was carried out in absence of ethyl isocyanoacetate under PTC conditions and the poor recovery (28%) of the starting bromide **4** was observed. To improve the yield of **11**, alkylation reaction was attempted under different reaction conditions. For example, alkylation of ethyl isocyanoacetate with bromide **4** under NaH/DMSO conditions gave the low yield of the product **11** when compared to PTC conditions. It is known that the phosphazene bases improve the yields of the coupling product when sensitive substrates are involved where the unwanted side reactions are minimized.[8] In this regard, 2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine (BEMP) has been used as a base in acetonitrile at 0 °C and the coupling product **11** was isolated in 14% yield (4-fold increased as compared to PTC conditions) as an isomeric mixture. Hydrolysis of the isonitrile derivative **11** in presence of HCl/diethyl ether gave the *trans* form of *N*-formyl derivative **12** (mp 210 °C decomp.) in 48% isolated yield, whose structure has been determined by X-ray crystallography studies and another isomer **13** (mp 220°C decomp.) in 40% isolated yield. ^{13}C NMR spectral data of *trans* isomer **12** (δ 14.2, 34.7, 40.0, 62.0, 66.7, 128.5, 129.3, 133.2, 138.9, 160.7, 171.8) supported the formation of **12**. The structure of *trans* isomer **12** was further supported by FAB mass spectral data (675 M + 1) and single crystal X-ray studies.[9] The 11-line ^{13}C NMR spectral data of **13** (δ 14.2, 34.0, 39.8, 62.0, 68.0, 128.4, 128.9, 133.0, 138.6, 161.5, 172.3) and FAB mass spectral data (675 M + 1)



Scheme 3. (i) $CNCH_2CO_2CH_2CH_3$, K_2CO_3, CH_3CN, Δ or BEMP CH_3CN, 0 °C; (ii) H^+, ether, 0 °C –rt.

supported the formation of another isomeric product relating to **12**. The structure of **13** has not been determined by X-ray studies at this point. In conclusion, for the first time we have synthesized the cyclophane-based unusual α-amino acid derivative **11** by PTC conditions and in this regard BEMP base was found to be useful for alkylation of ethyl isocyanoacetate to generate macrocyclic cyclophane derivative without high dilution conditions. The macrocyclic amino acid derivatives prepared here may find useful applications in bioorganic chemistry with regard to molecular recognition.

Acknowledgements

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5. Yields refer to overall yield starting from the dibromide **4**.

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9. The details will be published elsewhere. A typical experimental procedure for alkylation of ethyl isocyanoacetate in presence of BEMP: To a stirred solution of bromide **4** (130 mg, 0.35 mmol) and ethyl isocyanoacetate (40 mg, 0.35 mmol) in dry acetonitrile (3 mL) was added dropwise BEMP (193 mg, 0.7 mmol) in actonitrile (1 mL) at 0 °C under nitrogen. Then, the reaction mixture was brought at room temperature and stirred for 30 min. The solvent was evaporated under reduced pressure and then extracted with diethyl ether (20 mL×3). The combined organic layer was washed with water (20 mL), brine (20 mL) and dried over anhydrous $MgSO_4$. Evaporation of the solvent gave the crude product which was charged on a silica gel column. Elution of the column with 5% ethyl acetate/petroleum ether mixture gave 16 mg (14%) of the coupling product **11**.

The hydrolysis sequence of **11** was carried out in presence of HCl in diethyl ether (0 °C to room temperature) to deliver the *N*-formyl derivatives **12** and **13**.