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SYNTHESIS OF CONFORMATIONALLY CONSTRAINED α-AMINO ACID DERIVATIVES USING ETHYL ISOCYANOACETATE AS GLYCINE EQUIVALENT [1]

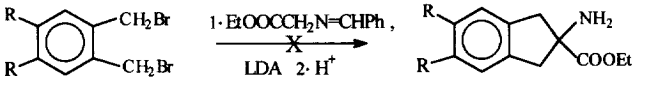
Sambasivarao Kotha*, and Enugurthi Brahmachary

Department of Chemistry, Indian Institute of Technology, Powai, Mumbai-400 076, India

Abstract: Some novel cyclic α-amino acid derivatives are prepared under solid-liquid phase-transfer catalytic conditions. Some of these amino acids prepared here are not directly accessible by the known methods.

Over the years unusual α-amino acids (AAAs) [2] have been found to play a significant role in the interface of chemistry, and biology. For example, incorporation of unusual AAAs into peptides has led to unique analogues which are biologically more active and resistant to enzymatic degradation.[3] Unique conformational properties can also be introduced in a peptide chain through proper elaboration of a suitable amino acid precursor.[4] With the availability of new techniques in molecular biology, it may be possible to generate more effective therapeutics or elucidate structure-activity relationship *via* incorporation of unusual AAAs into proteins.[5] Preparation of AAAs also extends the availability of building blocks towards the synthesis of natural products and drugs.[6]

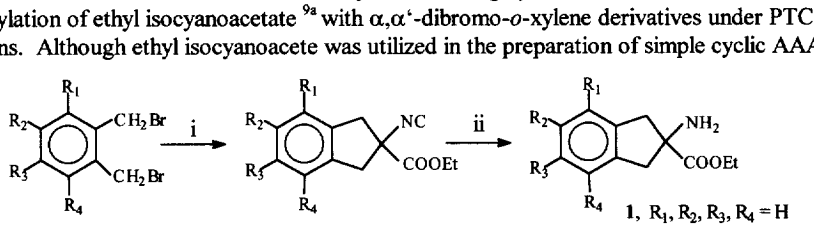
Numerous synthetic methods are available for the preparation of simple acyclic AAAs,[7] while only a limited number of methods are applicable for cyclic AAAs with the exception of simplest five and six membered compounds. The conventional method for the preparation of the cyclic AAA derivatives involving Bucherer-Berg (BB) method has many limitations. The starting materials required for BB method involve a multistep sequence and hydrolysis of intermediate spiro-hydantoins further requires drastic reaction conditions (excess barium hydroxide, 140 °C, or 60% sulfuric acid 140 °C). Consequently, it is very difficult to prepare amino acids with sensitive side chain functionalities by the BB method. Amino acid derived from compound **1**, a cyclic analogue of phenylalanine was utilized in the synthesis of angiotensin II receptor with agonistic and antagonistic activity. [8]



(eq. 1)

R = Electron withdrawing group or halogen atom

We attempted the synthesis of various unusual AAAs where conventional methods [e.g., Bucherer-Berg method or alkylation of Schiff base derived from glycine ester (eq 1)] fail. In this communication we describe our results for the syntheses of highly functionalised AAA derivatives which involve alkylation of ethyl isocyanoacetate [9a] with α,α'-dibromo-*o*-xylene derivatives under PTC (Scheme 1) conditions. Although ethyl isocyanoacete was utilized in the preparation of simple cyclic AAAs



1, $R_1, R_2, R_3, R_4 = H$

Scheme 1. i. $CNCH_2COOEt$, K_2CO_3, PTC, CH_3CN / reflux ii. HCl

under NaH-DMSO/ether conditions it was not feasible to extend to complex systems. We found that ethyl isocyanoacetate can be effectively used as a glycine equivalent in the synthesis of electronically interesting AAAs under solid-liquid phase transfer conditions. [9b]

Various substrates that have undergone succesful intramolecular coupling reaction are shown in Table 1. Some aspects of this intramolecular alkylation process are noteworthy. In general, cyclization reaction proceeded smoothly in a range of substrates. It is interesting to note that substrates containing electron donating (entry No.2) as well as electron withdrawing groups (entry Nos. 6 & 7) had undergone intramolecular alkylation reaction to deliver the required coupling products. The most striking example in the present study is the synthesis of pyrene-derived amino acid derivative **2** (entry No.6) containing electron withdrawing groups. It is known that substrates containing electron withdrawing groups (e.g., **3**) undergo dimerization reactions *via* single electron transfer pathway to give unwanted dimer instead of the required coupling product when sodium or lithium-based reagents (e.g., LiHMDS) were used during alkylation step. The present methodology allows us to prepare the highly electron deficient AAA derivative (entry No.6) without involvement of any protecting groups and thereby reducing the number of steps considerably.[10]

This methodology is also applicable for the synthesis of quinone-based AAA derivative such as **4**. Since quinones of diverse nature play an important role as components of the biological electron transport chains in both photosynthetic and respiratory membrane systems, this methodology may find useful application in designing artificial photosynthetic probes.[11, 12] Our successful synthesis of **2** and **4** may serve as an illustrative examples for other electron deficient AAAs yet to be explored. AAA containing halogen atoms (e.g. **5**) which is not accessible by Schiff-base methodology, (or BB method) opens up new possibilities for further synthetic exploration. Hydrolysis of the coupling products was performed efficiently by simply treating the isonitrile compounds in ethanolic HCl at room temperature for few hours (yields : 60-95%).

In summary, we have shown that the ethyl isocyanoacetate can easily be alkylated with the readily accessible α,α'-dibromo-*o*-xylene derivatives in acceptable yields. The flexibility of this method has been demonstrated *via* the syntheses of diverse AAA derivatives. Moreover, commercial availability of ethyl isocyanoacetate combined with the operational simplicity makes this methodology extremely attractive for the preparation of highly functionalised AAAs.

A typical experimental procedure for coupling of ethyl isocyanoacetate with dibromo derivatives can be illustrated with entry no. 6: A solution of dibromide **3** (100 mg, 0.24 mmol), ethyl isocyanoacetate (27.5 mg, 0.24 mmol), potassium carbonate (199 mg, 1.4 mmol) and tetrabutylammonium hydrogen sulfate (24.4 mg, 0.07 mmol) in acetonitrile (7 ml) was refluxed for 3 h. Then the reaction mixture was cooled and filtered through a sintered glass crucible to remove the unwanted salts and the filtrate was evaporated under reduced pressure. The residue was taken in ether (30 ml) and washed with water (20 ml), brine (20 ml) and dried over $MgSO_4$. Evaporation of solvent followed by column chromatography (silica gel) and crystallization from ethyl acetate- hexane mixture (1:3) afforded light brown crystalline needles **2** (35.5 mg, 40 %). mp. 172-173 °C; IR (KBr) ν 2140 cm^{-1} (N≡C), 1746 cm^{-1} (COOEt); ^1H NMR (300 MHz, $CDCl_3$) δ 1.38 (t, *J*=7.14 Hz, 3H, $OCH_2\underline{CH_3}$), 1.53 (d, *J*=2.01 Hz, 6H, $C\underline{H_3}$), 3.68 (part of ABq, *J*=16.3 Hz, 2H, $\underline{H}CH$), 3.8 (part of ABq, *J*=16.6 Hz, 2H, $HC\underline{H}$), 4.38 (q, *J*=7.11 Hz, 2H, $OC\underline{H_2}CH_3$), 7.6 (d, *J*=7.32 Hz, 2H, Ar-$\underline{H}$), 8.41 (d, *J*=7.5 Hz, 2H, Ar-$\underline{H}$). ^{13}C NMR (75.4 MHz,$CDCl_3$) δ 13.5 (q), 22.4 (q), 23.2 (q), 40.0 (t), 58.7 (s), 61.4 (s), 63.6 (t), 126.5 (s), 126.5 (d), 126.6 (s), 129.0 (d), 131.1 (s), 136.6 (s), 160.1 (s), 167.5 (s),198.7 (s); Mass : M^+ 361.

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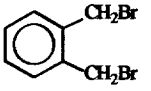
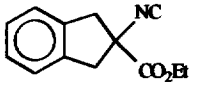
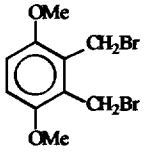
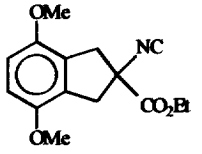
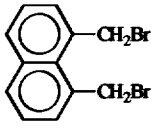
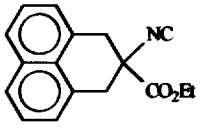
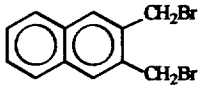
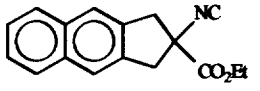
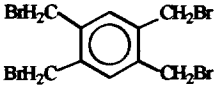
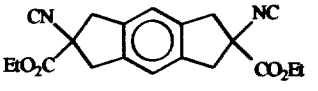
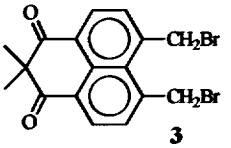
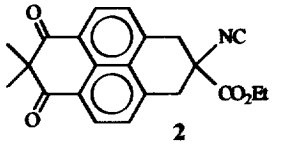
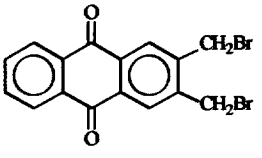
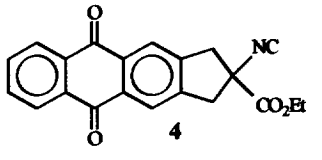
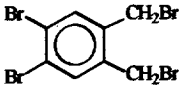
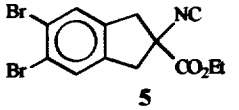
Table 1: Synthesis of various α-amino acid derivatives. Hydrolysis of all these products gave amino esters (60-95 %)

Entry No.	Electrophile	Coupling Product	mp / yield
1			60-62 °C 93 %
2			97-98 °C 57 %
3			74-75 °C 89 %
4			138-139 °C 65 %
5			167-168 °C 154-156 °C cis-trans isomers combined 42 %
6	 3	 2	172-173 °C 40 %
7		 4	207-208 °C 42 %
8		 5	59-60 °C 65 %

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