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Design and Synthesis of Pyrene Containing Unusual α-Amino Acid Derivatives

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[+] - Recorded the single crystal X-ray data

Abstract

We report here, constrained α-amino acid derivatives containing pyrene ring by using ethyl isocyanoacetate as a glycine equivalent. The required starting precursor 1,4,5,8-tetrakis(bromomethyl)naphthalene **14** was prepared starting with commercially available naphthalene-1,4,5,8-tetracarboxylic anhydride **15** in a three step sequence.

Keywords

Esterification, reduction, ethyl isocyanoacetate, hydrolysis, *N*-acylation, amino acid.

Introduction

Natural products and their derivatives are useful source for drug discovery; however they have limited solubility and some undesirable properties. Unusual α-amino acids (AAAs) are useful to modify peptide drugs. The incorporation of unusual AAA into peptides containing protenogenic amino acids is known to improve the performance of these molecules and minimize side effects [1]. Unusual AAA plays an important role in medicinal chemistry and they act as useful building blocks to design critical drugs and they play an important role in design of biologically active peptides [2-5]

and peptidomimetics. They can be introduced in peptide chains and easily combined with the aid of amine and carboxyl groups and they are important tools in of modern medicinal chemistry [6-8]. Moreover, cyclic peptides, antibiotics, antimicrobial peptides, anticancer agents contain various unusual AAA derivatives as critical components [9-11].

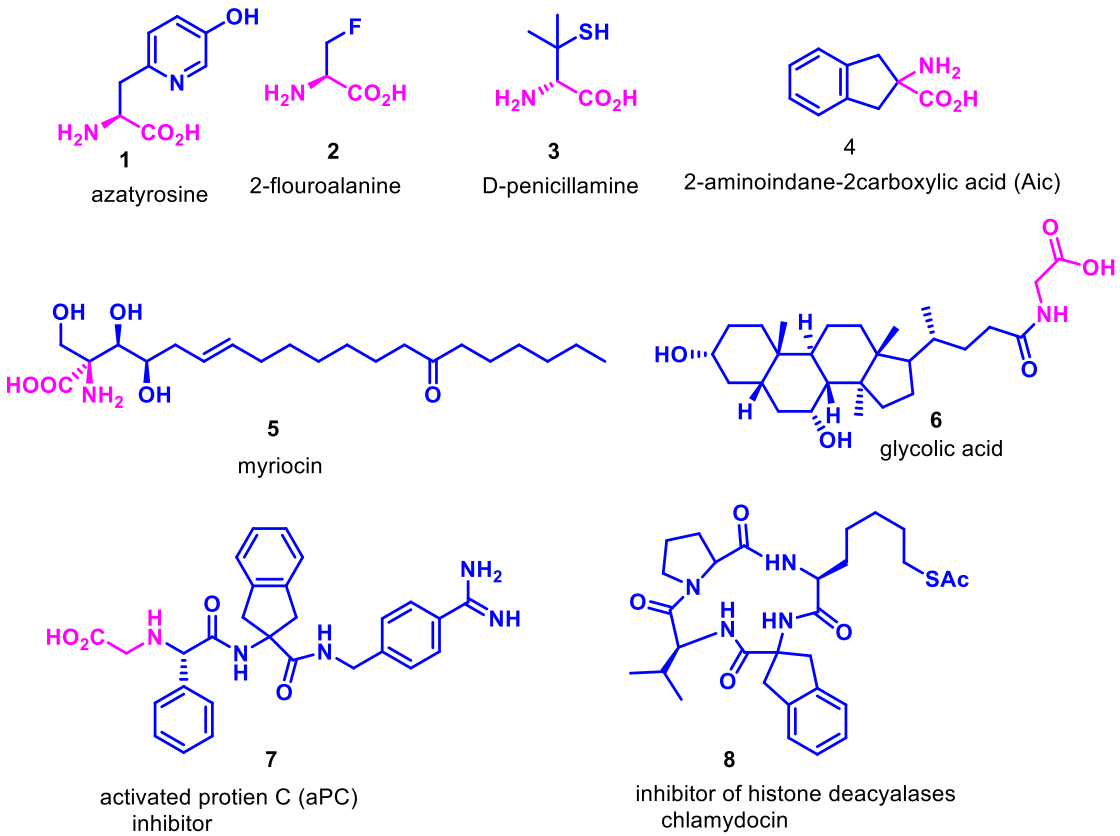


Figure 1. Examples of bioactive amino acid and peptides

Recently these synthons are found to be valuable in drug discovery and play critical role in design of therapeutic agents [12-14]. Massoud and co-workers reported structural analogue of OM00-3 containing AAAs [15]. The enduracididine [16,17] is a special class of amino acids which contain guanidine unit. Some bioactive free amino acids and peptides (**1-8**) like azatyrosine 1, *β*-flouroalanine **2** and D-penicillamine **3** are examples of unusual AAA derivatives [18].

Myriocin **5** is natural product containing amino acid synthesized by Miroslava and co-workers prepared this unusual AAA derivative which is found to be useful as a antifungal agent [19]. Glycolic acid **6** shows anticancer activity, compound **7** act as a protein inhibitor and compound **8** is inhibitor of histone deacyalases (Figure 1) [20,21].

Kotha and Lahari synthesized phenylalanine based unusual AAAs and peptides [22]. Constrained AAAs were also synthesized using cross enyne metathesis [23]. They also synthesized amino acid derivatives by using diethyl acetamidomalonate (DEAM) as a glycine equivalent (Figure 2) [24].

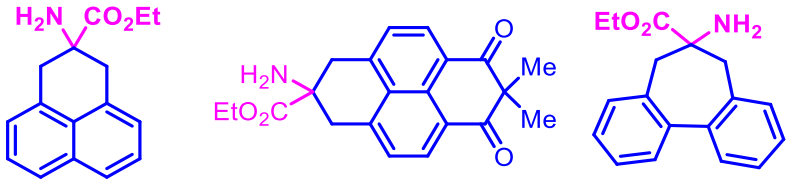


Figure 2. Examples of constrained unusual amino acid derivatives

In view of importance of AAAs in drug design and medicinal chemistry we aim to synthesize polycyclic amino acid derivatives such as **12** containing pyrene unit by using ethyl isocyanoacetate as a glycine equivalent that can be useful to expand the library of cyclic unusual AAA derivatives.

The retrosynthetic analysis of AAA derivative **12** is shown in Figure 3. The protected amino acid derivative **12** can be synthesized via hydrolysis of isonitrile derivative **13**. The required isonitrile derivative **13** can be obtained by intramolecular alkylation of ethyl isocyanoacetate with tetrabromide **14**. Interestingly, 1, 4, 5, 8 tetrakisbromomethyl naphthalene **14** can be prepared via bromination of tetrahydroxy naphthalene **17**, which can be derived from naphthalene anhydride **15** involving reduction as a key step.

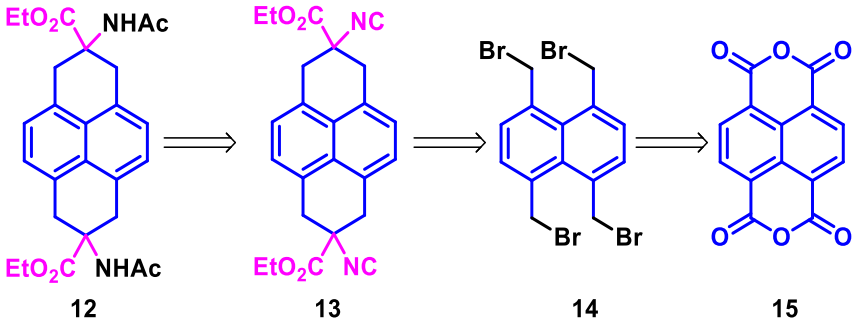
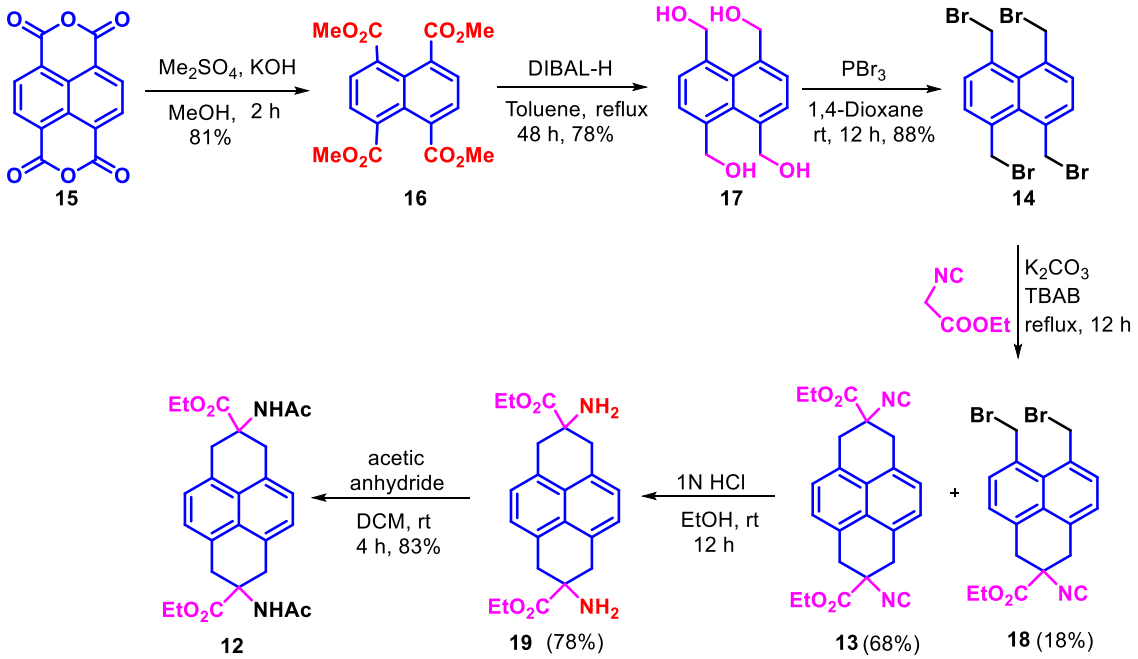


Figure 3. Retrosynthetic analysis of amino acid derivative **12**

The retrosynthetic path towards the target AAA derivative **12** require the key intermediate, 1, 4, 5, 8 tetrakisbromomethyl naphthalene **14**. It can be easily prepared by bromination of alcohol **17** with phosphorous tribromide in 1,4 dioxane. In this regard, reduction of tetraester **16** with diisobutylaluminium hydride (DIABAL-

H), prepared from naphthalene anhydride **15** by hydrolysis and methylation using dimethyl sulphate [25,26]. 1, 4, 5, 8 Tetrakisbromomethyl naphthalene **14** was converted to isonitrile derivative **13** by reacting with ethyl isocyanoacetate- in the presence of potassium carbonate in acetonitrile to produce the mono **18** and di isonitrile **13** derivatives [27-32]. Here, the interesting aspect of compound **13** is we observe two shapes of crystals under microscope. Later, we confirmed their structures by X-ray diffraction study and these two compounds (rod and dumbbell shaped) were found to be *cis* and *trans* isomers **13** and **13a** containing both ester and isonitrile groups. The hydrolysis of diisonitrile derivative **13** with HCl produced amino acid derivative. Hydrolysis followed by *N*-acylation gave 83% yield of acetyl derivative **12** (Scheme 1).



Scheme 1. Synthesis of amino acid derivative **12**

In Scheme 1 compound **13** we got two diastereomer *cis* and *trans* mixture.

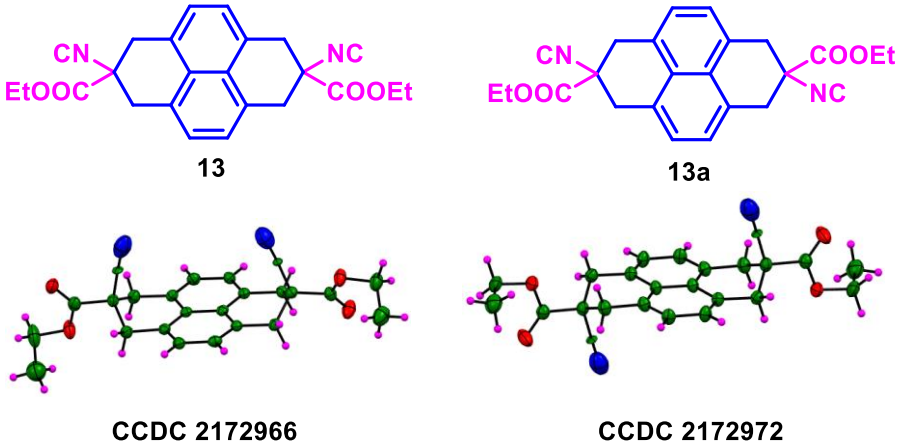
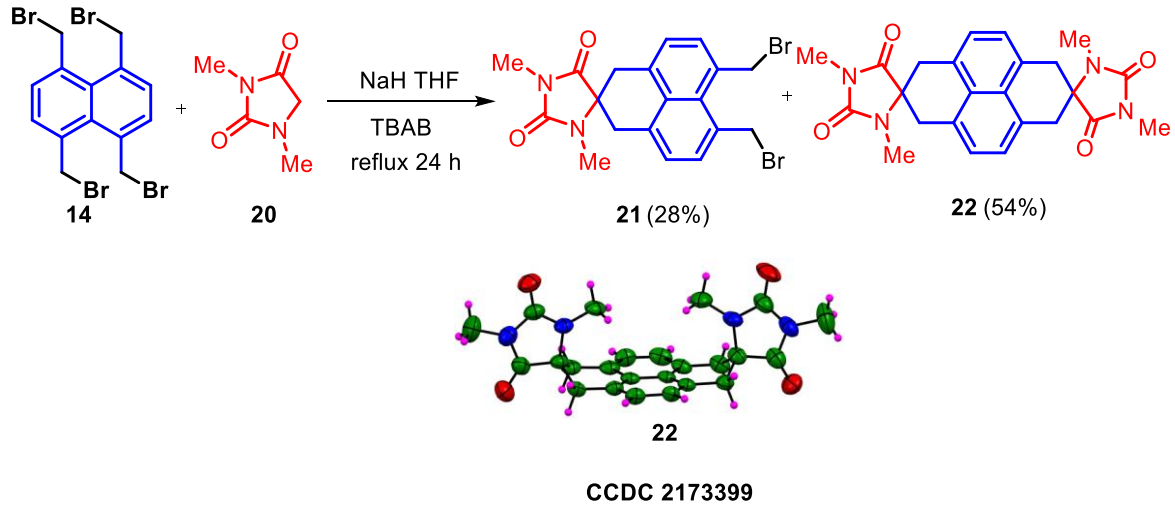


Figure 4. Single-Crystal XRD structure of compounds **13** and **13a**

To expand the coupling strategy, to naphthalene tetrabromide **14** was coupled with different active methylene compounds like, *N,N*-dimethyl hydantoin [33] and *N*-methyl thiazolidine. In this context, treatment of tetrabromo compound **14** with hydantoin derivative **20** in the presence of NaH in THF gave the mono **21** and the di coupled hydantoin derivative **22**.



Scheme 2. Synthesis of spiro compounds **21** and **22**

Structure of compound **22** was also confirmed by a single crystal X-ray diffraction study. Based on this data compound **22** was found to have a boat like structure. Unfortunately, with thiazolidine derivative we didn't observed the coupling product under the same reaction conditions (NaH, THF).

Conclusion

In conclusion, we successfully synthesized AAA containing pyrene ring system using ethyl isocyanoacetate as a glycine equivalent. These new AAA derivatives are likely to find useful applications in medicinal chemistry. We also reported the cis and trans isomers of isonitrile derivatives and these structures are established a by single crystal X-ray diffraction studies and the structure of hydantoin derivative **22** was also confirmed by single crystal X-ray diffraction studies and it shows boat shape structure.

Supporting Information

File 1:

General information, characterization data, copies of NMR spectra, X-ray data and refinement parameters.

File 2: CIF Files (Compounds **13, 13a, 22**)

Acknowledgements

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