Synthesis of Indan-Based Unusual α-Amino Acid Derivatives under Phase-Transfer Catalysis Conditions

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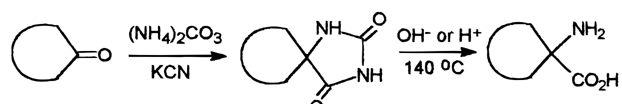
Conformationally constrained cyclic α-amino acid derivatives were synthesized under solid-liquid phase-transfer catalysis conditions. This methodology involves the bis-alkylation of ethyl isocyanoacetate with various α,α′-dibromo-*o*-xylene derivatives [α,α′-dibromo-*o*-xylene **5**, 2,3-bis(bromomethyl)-1,4-dimethoxybenzene **6**, 1,2-bis(bromomethyl)-4,5-dibromobenzene **7**, 2,3-bis(bromomethyl)-naphthalene **8**, 1,8-bis(bromomethyl)-naphthalene **9**, 6,7-bis(bromomethyl)-2,2-dimethyl-1*H*-phenalene-1,3(2*H*)-dione **10**, 2,3-bis(bromomethyl)-1,4-anthraquinone **11**, 6,7-bis(bromomethyl)quinoxaline **12**, 3,4-bis(bromomethyl)furan **13**, 1,2,4,5-tetrakis(bromomethyl)benzene **28**, and hexakis-(bromomethyl)benzene **30**] using potassium carbonate as a base and tetrabutylammonium hydrogensulfate as a phase-transfer catalyst to give corresponding isonitrile derivatives, which upon hydrolysis with HCl in ethanol gave amino esters. Using this method electron-deficient as well as electron-rich and halogen-substituted indan-based α-amino acids were prepared. The preparation of bis-indan as well as tris-indan α-amino esters is also described.

Introduction

Peptide backbone conformation or secondary structure is crucial in the design of peptide-based therapeutics.[1] In this regard α,α-dialkylated amino acids play an important role in the design of conformationally restricted peptides.[2,3] Cyclic α-amino acids[4] (AAAs) are considered as a special class of α,α-dialkylated amino acids, and surprisingly only the simplest members of this class had been used in the peptide arena. This is due to the nonavailability of synthetic methods to deliver complex cyclic AAAs.

Synthetic methods that are available for the preparation of simple cyclic five- and six-membered AAAs are not applicable for the preparation of functionalized AAAs. The traditional Bucherer−Berg (BB) method[5] involves the conversion of a cyclic ketone into a spirohydantoin under potassium cyanide and ammonium carbonate conditions. Hydrolysis of the spirohydantoin either in basic conditions (excess barium hydroxide in water, 140 °C) or in acidic conditions (60% H_2SO_4, 140 °C) gives cyclic AAAs (eq 1). Though the BB method provides an easy access to many cyclic and polycyclic AAAs from corresponding keto derivatives, the harsh conditions required for the hydrolysis of the hydantoin intermediate limits this method to prepare functionalyzed AAAs. However, recently Kubic et al. reported a mild and facile hydrolysis of a di-Boc derivative of spirohydantoin under basic conditions (LiOH/THF/H_2O/rt) to give AAAs.[5b]



(eq 1)

O'Donnell et al.[6a] developed a simple method for unusual AAAs synthesis, which involves alkylation of a Schiff base derived from glycine ester with various electrophiles, under phase-transfer catalyst (PTC) conditions. Although this method is applicable for simple AAA derivatives, it was not extended to the synthesis of complex cyclic AAAs.

The alternate methodology[6b] for cyclic AAAs involves intramolecular cyclization of α,α′-dibromo-*o*-xylenes with a Schiff base derivative of glycine ethyl ester using lithium or sodium hexamethyldisilazane (NaHMDS) as a base during the alkylation step (eq 2). The major limitation of this method is inapplicability for substrates

† Abstracted from the Ph.D. Thesis of E. Brahmachary, Indian Institute of Technology-Bombay, 1999.

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(2) For leading references, see: Toniolo, C.; Benedetti, E. *Macromolecules* **1991**, *24*, 4004. Tonilolo, C.; Crisma, M.; Formaggio, F.; Valle, G.; Cavicchioni, G.; Precigoux; Aubry, A.; Kamphuis, J. *Biopolymers* **1991**, *31*, 1061. Balaram, P. *Curr. Opin. Struct. Biol.* **1992**, *2*, 845. Hruby, V. J.; Al-Obeidi, F.; Kazmierski, W. *Biochem. J.* **1990**, *268*, 249. Paradisi, M. P.; Torrini, I.; Zecchini, G. P.; Lucente, G.; Gavuzzo, E.; Mazza, F.; Pochetti, G. *Tetrahedroin* **1995**, *51*, 2379.

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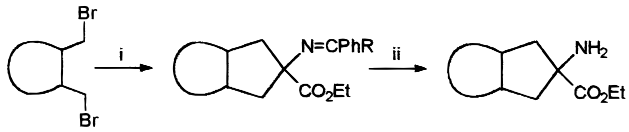
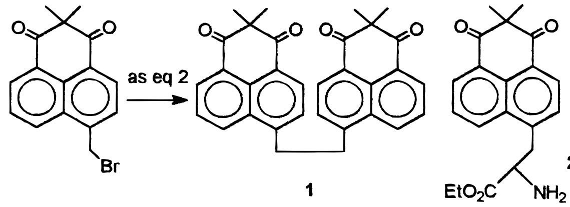


Reagents: i. $RPhC{=}NCH_2CO_2Et$, NaHMDS, THF ii. HCl. EtOH (eq 2)

having halogens or electron-withdrawing groups in the aromatic ring. For example, substrates containing electron-withdrawing groups undergo dimerization reaction via a single-electron-transfer pathway to give unwanted dimers (e.g., **1**) instead of the alkylation products (e.g., **2**, eq 3).[7] A slight modification of the Schiff base method



(eq 3)

was appeared recently by using solid-supported Schiff base and 20-fold excess of dibromide and also similar excess of NaHMDS as a base.[8] But this method could deliver only moderate yields of the coupling product, and there was no evidence for reactive functional group tolerance.

Among the constrained phenylalanine (Phe) analogs, indan-based AAAs play a crucial role in the design of a variety of bioactive peptides.[9−11] For example 2-aminoindan-2-carboxylic acid **3** (Ind) was utilized in the synthesis of molecules with angiotensin II receptor agonistic and antagonistic activity. In view of the several other applications of Ind derivatives and problems associated with the existing methods to generate Ind derivatives with varying shape, size, and electronic properties, we sought a process that is not restricted to a simple substitution pattern and also would be sufficiently flexible to generate various unusual AAAs. In this report we disclose full details of our facile and simple synthesis of indan-based unusual AAAs under solid−liquid PTC conditions using ethyl isocyanoacetate as a glycine equivalent.

Strategy

Toward the synthesis of 2-aminoindan-2-carboxylic acid **3** (Ind) starting from the preformed benzene derivatives, two possible routes were identified. Alternate strategies involving benzene ring formation via a cycloaddition reaction are not included here. Retrosynthetic analysis of these routes are shown in Figure 1.

Path a is an example of Bucherer−Berg synthesis of cyclic AAAs and requires a multistep synthetic sequence for starting 2-indanone derivatives (e.g., **4**). The limited number of easily available 2-indanone derivatives and the involvement of the drastic reaction conditions makes this route less attractive for the preparation of highly functionalized Ind derivatives. Path b involves bis-alkylation of glycine or an appropriate glycine equivalent with α,α′-dibromo-*o*-xylene **5**. Since several α,α′-dibromo-*o*-xylene derivatives are easily available or can be prepared from the readily available starting materials, this route deserves a systematic investigation.

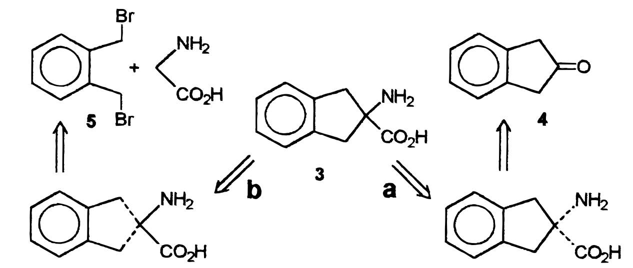


Figure 1.

Results and Discussion

Adaptation of approach b to the synthesis of indan-based AAAs requires preparation of α,α′-dibromo-*o*-xylene derivatives as starting materials. All the dibromides (**6**−**13**) used in the present study were obtained by standard/modified literature procedures.

2,3-Bis(bromomethyl)-1,4-dimethoxybenzene **6** was prepared from 2,3-dimethylhydroquinone via the *o*-methylation and bromination sequence.[12] Similarly, 2,3-bis(bromomethyl)naphthalene **8** and 1,8-bis(bromomethyl)naphthalene **9** were prepared from the corresponding dimethylnaphthalenes. 1,2-Bis(bromomethyl)-4,5-dibromobenzene **7** was synthesized starting from *o*-xylene in a two-step sequence.[13]

The new phenalene-derived dibromide **10** that was required for the preparation of highly electron-deficient pyrene-based AAA was obtained from 1,8-dimethylnaphthalene **14** in a two-step sequence. Thus, the reaction of compound **14** with dimethylmalonyl dichloride in the presence of aluminum chloride in nitrobenzene gave compound **15** (45%; mp, 105−107 °C) as a major product (eq 4). Formation of less-strained six-membered ring isomer **15** over the other possible five-membered ring isomers **16** and **17** in the Friedel−Crafts (FC) reaction is expected to be thermodynamically more favorable. However, Dolbier et al. have shown that the solvent has a dramatic effect on the product distribution in FC reaction of this type of substrates.[14] The compound **15** was characterized by its symmetrical ^1H and ^{13}C NMR spectral data. The other two isomers were also identified on the basis of ^1H NMR spectral data. The reaction of **15** with NBS/AIBN in carbon tetrachloride gave the dibromide **10** (86%; mp, 175−176 °C).

Benzylic bromination of known 2,3-dimethylanthraquinone[15] using NBS gave 2,3-bis(bromomethyl)-1,4-

(7) Kotha, S.; Kuki, A. *Tetrahedron Lett.* **1992**, *33*, 1569.
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(10) (a) Torrini, I.; Zecchini, G. P.; Paradisi, M.; Lucente, G.; Gauzzo, E.; Mazza, F.; Pochetti, G.; Spisani, S.; Giuliani, A. L. *Int. J. Pept. Protein Res.* **1991**, *38*, 495. (b) Hsieh, K.-h.; Jorgensen, E. C. *J. Med. Chem.* **1979**, *22*, 1038.
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(14) Dolbier, W. R., Jr.; Dulcere, J.-P.; Sellers, S. F.; Koroniak, H.; Shatkin, B. T.; Clark, T. L. *J. Org. Chem.* **1982**, *47*, 2298.
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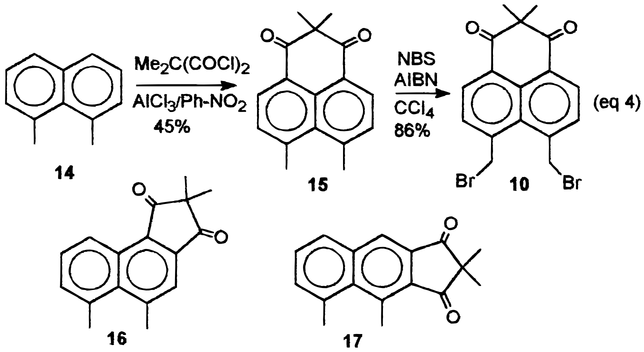
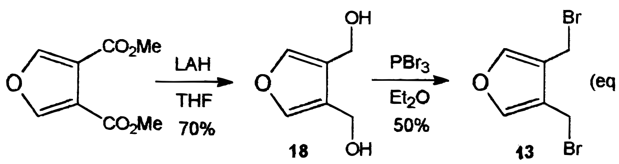


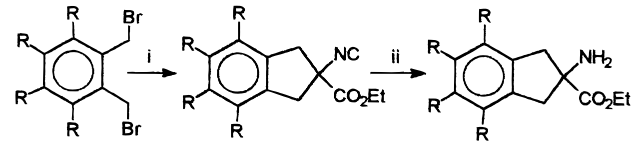
anthraquinone **11**. Similarly, synthesis of quinoxaline dibromide **12** was achieved from 6,7-dimethylquinoxaline.[16] The minor product obtained (most likely the monobromo or tribromo derivative) during the NBS reaction of 6,7-dimethylquinoxaline was highly unstable and could not be isolated in a pure form for the spectral characterization.

Lithium aluminum hydride reduction of dimethyl 3,4-furandicarboxylate in dry THF gave diol **18**.[17] Conversion of diol **18** to dibromide **13** was accomplished by phosphorus tribromide/pyridine reaction conditions (eq 5). Recently, Atasoy and co-workers synthesized compound **13** using a different route involving a five-step sequence.[17c]



From the earlier observation, electronically active dibromo-*o*-xylene derivatives were found to be sensitive to several conventional base conditions. In this regard solid−liquid PTC conditions appeared to be an attractive solution. Moreover, PTC conditions[18] offer an attractive way of preparing optically active products by using chiral PTCs.[19] After several amino acid synthons were screened, ethyl isocyanoacetate was realized as a potential glycine equivalent. It was found that the ethyl isocyanoacetate can be easily bis-alkylated in the presence of potassium carbonate as a base and tetrabutylammonium hydrogensulfate (TBAHS) as a PTC to give corresponding isonitrile derivatives (Scheme 1). It is interesting to note that there are not many examples known in the literature where ethyl isocyanoacetate was used as a glycine equivlanet.[20] Absence of water in the reaction medium provides an advantage, which avoids nucleophile substitution reactions leading to the formation of unwanted hydroxy compounds. By using liquid−liquid PTC conditions (40% NaOH/PTC/CH_2Cl_2), formation of dihydroxy or cyclic ether was observed in some instances. Reaction of α,α′-dibromo-*o*-xylene **5** with ethyl isocyanoacetate in the presence of potassium carbonate and TABHS in acetonitrile gave the required coupling product **19** (Table 1) in 93% isolated yield.

Scheme 1. i. $CNCH_2CO_2Et$, K_2CO_3, Bu_4NHSO_4, MeCN, Δ. ii. HCl, EtOH



Similarly, various dibromo derivatives that have effectively undergone the cyclization reaction with ethyl isocyanoacetate under PTC conditions are shown in Table 1.[21] In the absence of PTC, only 50% of the product **19** obtained. In some instances the yields are reduced much more drastically. The coupling products (**19**−**27**) were isolated by a silica gel column as crystalline solids and characterized by their characteristic ^{1}H and ^{13}C NMR spectral data. In the ^{1}H NMR spectrum, characteristic AB quartet resonating in the region of δ 3−4 due to the diastereotopic methylene hydrogens indicated the formation of cyclized products. The isonitrile derivatives are hydrolyzed efficiently in a mild reaction condition (HCl/ethanol) to give amino esters in good yields. By varying the hydrolysis conditions, various protected forms of amino acid derivatives can be obtained.[22] For example, treatment of isocyano esters with HCl in ether at −10 °C will give *N*-formyl amino esters, whereas *N*-formyl amino acids can be obtained under KOH/ethanol/−10 °C conditions.

In general, the cyclization reaction proceeds well in a wide range of substrates without any complications. It is interesting to note that substrates containing electron-donating (entry 2) and electron-withdrawing groups (entries 6 and 7) also underwent the alkylation reaction to give the corresponding isonitrile derivatives. Cyclization was effective for both five-membered as well as six-membered ring (entries 5 and 6) formation. Since in recent years much attention was paid to synthsize amino acids possessing heterocyclic ring systems for various biological applications,[23,24] we have also extended our methodology to heterocyclic AAA derivatives (entries 8 and 9). Prior to these reaction conditions, synthesis of the quinoxaline-based AAA from bromide **12** under different reaction conditions (KO^{t}Bu, 40% aqueous NaOH, LDA, NaHMDS, KHMDS) gave unacceptable yields of

(16) Compound **12** reported as a liquid in the literature: Baudy, R. B.; Greenblatt, L. P.; Jirkovsky, I. L.; Conklin, M.; Russo, R. J.; Bramlett, D. R.; Emrey, T. A.; Simmonds, J. T.; Kowal, D. M.; Stein, R. P.; Tasse, R. P. *J. Med. Chem.* **1993**, *36*, 331.

(17) (a) Cook, M. J.; Frobes, E. J. *Tetrahedron* **1968**, *24*, 4501. (b) Reduction of diethyl 3,4-furandicarboxylate to diol **18**, see: Jenneskens, L. W.; Kostermans, G. B. M.; ten Brink, H. J.; de Wolf, W. H.; Bickelhaupt, F. *J. Chem. Soc., Perkin Trans 1* **1985**, 2121. (c) Atasoy, B.; Ozen, R. *Tetrahedron* **1997**, *53*, 13867.

(18) Starks, C. M.; Liotta, C. *Phase Transfer Catalysis: Principles and Techniques*; Academic Press: New York, 1978. Weber, W. B.; Gokel, G. W. *Phase Transfer Catalysis in Organic Synthesis*; Springer-Verlag: Berlin, 1977. Sirovski, F.; Reichardt, C.; Gorokhova, M.; Ruban, S.; Stoikova, E. *Tetrahedron* **1999**, *55*, 6363 and references cited therein.

(19) O'Donnell, M. J.; Bennett, W. D.; Wu, S. *J. Am. Chem. Soc.* **1989**, *111*, 2353. O'Donnell, M. J.; Wu, S.; Huffman, J. C. *Tetrahedron* **1994**, *50*, 4507.

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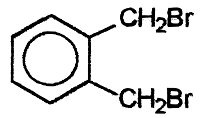
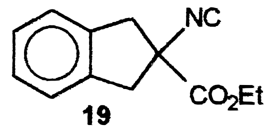
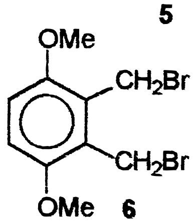
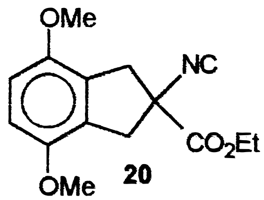
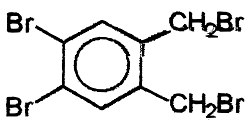
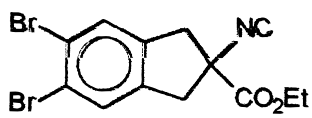
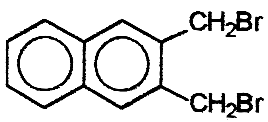
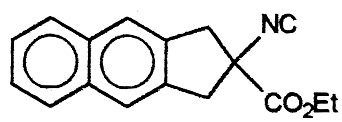
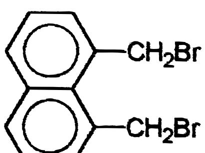
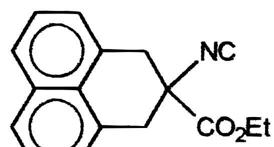
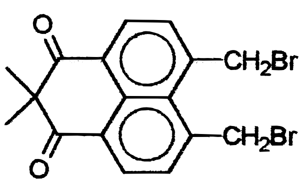
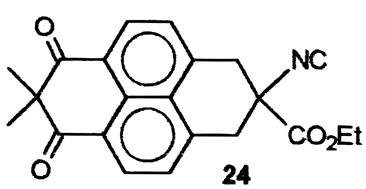
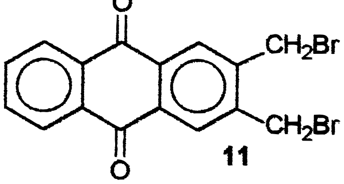
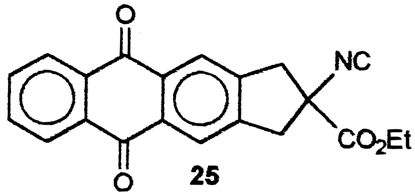
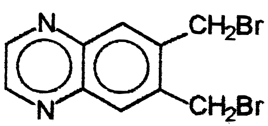
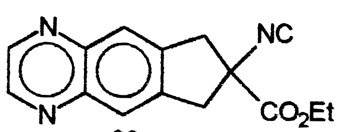
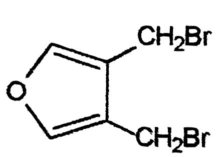
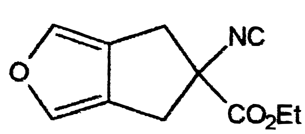
(22) Schollkopf, U.; Hoppe, D.; Jentsch, R. *Angew. Chem., Int., Ed. Engl.* **1971**, *10*, 331.

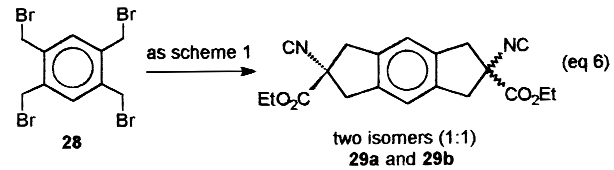
(23) Horwell, D. C.; McKiernan, M. J.; Osborne, S. *Tetrahedron Lett.* **1998**, *39*, 8729; Ma, C.; Liu, X.; Zhao, S.; Cook, J. M. *Tetrahedron Lett.* **1999**, *40*, 660. Franceschetti, L.; Garzon-Aburbeh, A.; Mahmoud, M. R.; Natalini, B.; Pellicciari, R. *Tetrahedron Lett.* **1993**, *34*, 3185. Bennett, F. A.; Barlow, D. J.; Dodoo, A. N. O.; Hider, R. C.; Lansley, A. B.; Lawrence, M. J.; Marriott, C.; Bansal, S. S. *Tetrahedron Lett.* **1997**, *38*, 7449.

Table 1. Synthesis of Cyclic α-Amino Acid Derivatives under Phase-Transfer Catalyst Conditions

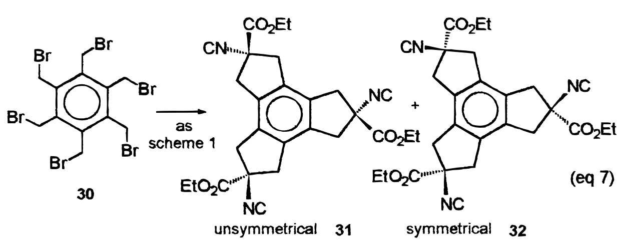
Entry No.	Electrophile	Coupling Product	mp / time / yield	Hydrol. Yield
1	 **5**	 **19**	60-62 °C 5h / 93 %	90 %
2	 **6**	 **20**	97-98 °C 3h / 57 %	88 %
3	 **7**	 **21**	59-60 °C 5h / 65 %	93 %
4	 **8**	 **22**	138-139 °C 4h / 65 %	96 %
5	 **9**	 **23**	74-75 °C 4h / 89 %	92 %
6	 **10**	 **24**	172-173 °C 3h / 40 %	90 %
7	 **11**	 **25**	207-208 °C 3h / 45 %	66 %
8	 **12**	 **26**	110-112 °C 3.5h / 40 %	94 %
9	 **13**	 **27**	40-42 °C 2.5h / 67 %	78 %

the coupling products (<5%). Usage of various amino acid synthons also met with no or little success. Finally by using solid–liquid PTC conditions, a highly base-sensitive dibromide **12** gave the required product **26** in 40% yield.[25] Since furan can undergo various cycloaddition reactions,[26] the derivative **27** may serve as a useful synthon for the generation of several other constrained AAA derivatives.

In the case of the tetrakis(bromomethyl)benzene **28**, two coupling products were obtained in 1:1 ratio, which were isolated by a silica gel column in 42% combined yield (eq 6). Both compounds (**29a** and **29b**) gave almost identical ^{1}H and ^{13}C NMR spectral data, and tentatively we concluded that they are cis/trans isomers. Independent hydrolysis of both isomers gave amino esters whose ^{1}H NMR spectra are again identical in nature.



Treatment of hexakis(bromomethyl)benzene **30** with ethyl isocyanoacetate under PTC conditions gave two trisindan derivaties (3:1, eq 7). Unlike the above indacene isomers, in this case both the stereochemically different isomers **31** and **32** could be distinguished by their ^{1}H NMR spectral data. The major isomer **31** (mp, 148−149 °C), isolated by a silica gel column, was confirmed by its ^{1}H NMR spectrum as an unsymmetrical compound. In the ^{1}H NMR spectrum, compound **31** gave a complex ABq resonating at δ 3.32 due to the diastereotopic methylene protons and a mixture of two triplets (2:1 ratio) and two quartets (2:1) due to ethyl ester functionality, suggesting its unsymmetrical nature. Compound **32** (mp, 120−121 °C) showed a symmetrical ABq due to methylene protons and a clean triplet and a quartet due to ethyl ester functionality in the ^{1}H NMR spectrum. Hydrolysis of these two isonitrile derivatives in a separate experiment gave amino esters as liquids in 80% yield. In view of recent developments in the utilization of multiarmed AAAs in the design and synthesis of new ligands and functional dendrimers, bis and tris-armed amino acid derivatives reported here may find interesting applications in chemical and allied sciences.[27]



Conclusions

In summary, we have shown that ethyl isocyanoacetate can be effectively bis-alkylated under solid−liquid PTC conditions with the readily available α,α′-dibromo-*o*-xylene derivatives. The flexibility of the method has been demonstrated via synthesis of simple as well as complex AAA derivatives. Moreover, commercial availability of ethyl isocyanoacetate combined with the operational simplicity makes this methodology extremely attractive for the preparation of highly functionalized AAAs. The ability to prepare electronically interesting AAAs will open the door to chemical, biological, and medicinal applications of unnatural AAAs.

Experimental Section

Melting points are uncorrected. Infrared spectra were recorded as KBr wafers unless mentioned otherwise. UV spectra were taken using chloroform as a solvent. ^{1}H NMR spectra were recorded at 300 or 60 MHz, and ^{13}C NMR spectra were recorded at 75.4 MHz. Samples were made in chloroform-*d* solvent, and chemical shifts were reported in δ scale using tetramethylsilane as the internal standard. Coupling constants *J* are in hertz (Hz). Analytical thin-layer chromatography (TLC) was performed on glass plates coated with Acme's silica gel G or GF 254 (containing 13% calcium sulfate as a binder). Visualization of the spots on the TLC plates was achieved by exposure either to iodine vapor or to UV light. Flash chromatography was performed using Acme's silica gel (100−200 mesh), and the column was usually eluted with hexane−ethyl acetate mixture. Acetonitrile and carbon tetrachloride were distilled over phosphorous pentoxide. Dry THF and ether were obtained by distillation over sodium benzophenone ketyl. For all the reactions dry magnesium sulfate was used as a drying agent after workup. Yields refer to the chromatographically isolated yields. *N*-Bromosuccinimide was freshly crystallized from hot water and dried under vacuum over P_2O_5 for 3 h. Ethyl isocyanoacetate, α,α′-dibromo-*o*-xylene **5**, tetrakis(bromomethyl)benzene **28**, hexakis(bromomethyl)benzene **30**, 4,5-dimethylphenalenediamine, 2,3-dimethylhydroquinone, dimethyl 3,4-furnadicarboxylate, 1,8-dimethylnaphthalene **14**, and dimethylmalonyl chloride were purchased from Aldrich Chemical Co. 2,3-Dimethyl naphthalene and lithium aluminum hydride were obtained from Lancaster Synthesis. All the commercial grade reagents were used without further purification.

General Procedure for the Bis-alkylation of Ethyl Isocyanoacetate. To a solution of ethyl isocyanoacetate (1 mmol) in acetonitrile (20 mL) were added finely grounded potassium carbonate (6 mmol), TBAHS (0.2 mmol), and electrophile (1 mmol). The resulting heterogeneous mixture was heated at 70−80 °C until all the starting electrophile had been consumed (TLC monitoring). Then, the reaction mixture was cooled and filtered through a cintered glass crucible to remove the unwanted salts. Then the solid material was washed with acetonitrile, and the filtrate was evaporated on a rotary evaporator under reduced pressure. The residue obtained was taken in ether and washed with water and brine and then dried. The solvent was evaporated, and the crude product was purified by silica gel column chromatography. Analytical samples were obtained by recrystallization from hexane and ethyl acetate mixture.

Precaution: *Ethyl isocyanoacetate and electrophiles used in this study are lacrymators and irritants and must be handled with proper care. Some of them are also potent mutagens.*

General Procedure for Hydrolysis of the Coupling Product. To a solution of the coupling product (1 mmol) in absolute ethanol (5 mL) were added a few drops of concentrated hydrochloric acid, and the reaction mixture was stirred at room temperature for a few hours. Ethanol was evaporated under reduced pressure, the remaining hydrochloride salt was dissolved in water and extracted with ether to remove unwanted organic residues, and the ether layer was discarded. Then the aqueous layer was brought to pH = 9−10 by addition of NH_4OH solution and then extracted with ethyl acetate. Combined ethyl acetate extract was washed with water and brine and dried. Removal of the solvent at reduced pressure gave amino ester.

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Ethyl 2-Isocyanoindan-2-carboxylate (19). Prepared from α,α′-dibromo-*o*-xylene **5** in 93% isolated yield as white crystalline needles. Mp, 60−62 °C. IR (KBr): ν 2139, 1746 cm^{-1}. UV ($CHCl_3$): λ_{max} nm (ϵ M^{-1} cm^{-1}) 273 (1810), 266 (1862). ^1H NMR: δ 1.35 (t, J = 7.2, 3H), 3.47 ($^1/_2$ ABq, J = 16.0, 2H), 3.69 ($^1/_2$ ABq, J = 16.3, 2H), 4.32 (q, J = 7.2, 2H), 7.25 (s, 4H). ^{13}C NMR: δ 14.0, 46.3, 63.1, 67.9, 124.6, 127.7, 137.9, 158.6, 168.6. MS: *m*/*e* 251 (M^+). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.08; N, 6.51. Found: C, 72.94; H, 6.05; N, 6.86. **Hydrolysis product:** Colorless liquid, 90%. IR (neat): ν 3350, 1725 cm^{-1}. ^1H NMR: δ 1.28 (t, J = 7.1, 3H), 1.81 (s, 2H), 2.92 ($^1/_2$ AXq, J = 15.6, 2H), 3.57 ($^1/_2$ AXq, J = 16.1, 2H), 4.22 (q, J = 7.1, 2H), 7.23 (m, 4H).

Ethyl 4,7-Dimethoxy-2-isocyanoindan-2-carboxylate (20). Prepared from 2,3-bis(bromomethyl)-1,4-dimethoxybenzene **6** as colorless plates in 57% yield. Mp, 97−98 °C. IR (KBr): ν 2133, 1749, 1255 cm^{-1}. UV ($CHCl_3$): λ_{max} nm (ϵ M^{-1} cm^{-1}) 281 (3550), 248 (2630). ^1H NMR: δ 1.34 (t, J = 7.1, 3H), 3.48 ($^1/_2$ ABq, J = 16.5, 2H), 3.61 ($^1/_2$ ABq, J = 16.6, 2H), 3.78 (s, 6H), 4.31 (q, J = 7.1, 2H), 6.69 (s, 2H). ^{13}C NMR: δ 13.9 (q), 44.0 (t), 55.5 (q), 63.0 (t), 67.7 (s), 109.9 (d), 127.4 (s), 149.9 (s), 158.3 (s), 168.6 (s). MS: *m*/*e* 275 (M^+). Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.08. Found: C, 65.91; H, 6.02; N, 5.13. **Hydrolysis product:** Light yellow liquid, 88%. IR (neat): ν 3373, 1727, 1257 cm^{-1}. ^1H NMR: δ 1.27 (t, J = 7.1, 3H), 2.77 (br s, 2H), 3.08 ($^1/_2$ AXq, J = 16.6, 2H), 3.48 ($^1/_2$ AXq, J = 16.5, 2H), 3.76 (s, 6H), 4.22 (q, J = 7.1, 2H), 6.65 (s, 2H).

Ethyl 4,5-Dibromo-2-isocyanoindan-2-carboxylate (21). Prepared from 1,2-bis(bromomethyl)-4,5-dibromobenzene **7** as a white crystalline solid in 65% yield. Mp, 59−60 °C. IR (KBr): ν 2139, 1741 cm^{-1}. ^1H NMR: δ 1.36 (t, J = 7.1, 3H), 3.41 ($^1/_2$ ABq, J = 16.5, 2H), 3.64 ($^1/_2$ ABq, J = 16.6, 2H), 4.33 (q, J = 7.1, 2H), 7.52 (s, 2H). ^{13}C NMR: δ 14.0, 45.4, 63.4, 68.1, 123.8, 129.7, 139.1, 159.7, 167.7; MS: *m*/*e* 373 (M^+). Anal. Calcd for $C_{13}H_{11}NO_2Br_2$: C, 41.85; H, 2.97; N, 3.75. Found: C, 41.85; H, 2.99; N, 3.51. **Hydrolysis product:** White crystalline solid, 93%. MP, 86−87 °C. IR (KBr): ν 3372, 1725. ^1H NMR: δ 1.29 (t, J = 7.1, 3H), 1.68 (br s, 2H), 2.81 ($^1/_2$ AXq, J = 16.1, 2H), 3.47 ($^1/_2$ AXq, J = 16.3, 2H), 4.22 (q, J = 7.1, 2H), 7.47 (s, 2H).

Ethyl 3-Isocyano-2,3-dihydro-4*H*-cyclopenta[*b*]naphthalene-3-carboxylate (22). Obtained as colorless plates from 2,3-bis(bromomethyl)naphthalene **8** in 65% yield. Mp, 138−139 °C. IR (KBr): ν 2140, 1746 cm^{-1}. UV ($CHCl_3$): λ_{max} nm (ϵ M^{-1} cm^{-1}) 321 (1890), 271 (3590). ^1H NMR: δ 1.36 (t, J = 7.1, 3H), 3.6 ($^1/_2$ ABq, J = 16.0, 2H), 3.83 ($^1/_2$ ABq, J = 16.3, 2H), 4.34 (q, J = 7.1, 2H), 7.45 (dd, J = 6.3, 3.1, 2H), 7.70 (s, 2H), 7.80 (dd, J = 6.2, 3.3, 2H). ^{13}C NMR: δ 14.0, 45.6, 63.2, 68.6, 123.2, 125.8, 127.7, 133.3, 136.5, 158.9, 168.3. MS: *m*/*e* 265 (M^{-1}). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.99; N, 5.28. Found: C, 76.89; H, 6.06; N, 5.09. **Hydrolysis product:** White crystalline solid, 96%. Mp, 75−76 °C. IR (KBr): ν 3367, 1722 cm^{-1}. ^1H NMR: δ 1.39 (t, J = 7.1, 3H), 1.67 (s, 2H), 3.03 ($^1/_2$ AXq, J = 16.1, 2H), 3.68 ($^1/_2$ AXq, J = 16.1, 2H), 4.25 (q, J = 7.1, 2H), 7.41 (m, 2H), 7.66 (s, 2H), 7.74 (m, 2H).

Ethyl 2-Isocyano-2,3-dihydro-1*H*-phenalene-2-carboxylate (23). Prepared from 1,8-bis(bromomethyl)naphthalene **9** as a colorless crystalline solid in 89% yield. Mp, 74−75 °C. IR (KBr): ν 2135, 1743 cm^{-1}. UV ($CHCl_3$): λ_{max} nm (ϵ M^{-1} cm^{-1}) 284 (1340), 277 (2650) nm. ^1H NMR: δ 1.34 (t, J = 7.1, 3H), 3.53 ($^1/_2$ ABq, J = 15.5, 2H), 3.69 ($^1/_2$ ABq, J = 15.7, 2H), 4.33 (q, J = 7.1, 2H), 7.30 (d, J = 6.9, 2H), 7.44 (t, J = 7.1, 2H), 7.77 (t, J = 8.2, 2H). ^{13}C NMR: δ 13.9 (q), 39.8 (t), 61.6 (s), 63.0 (t), 125.5 (d), 125.9 (d), 127.3 (d), 127.8 (s), 129.1 (s), 133.2 (s), 158.8 (s), 168.3 (s). MS: *m*/*e* 265 (M^+). Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.99; N, 5.28. Found: C, 76.82; H, 5.84; N, 5.42. **Hydrolysis product:** Colorless liquid, 92%. IR (KBr): ν 3374, 1730 cm^{-1}. ^1H NMR: δ 1.25 (t, J = 7.1, 3H), 1.62 (s, 2H), 1.15 ($^1/_2$ AXq, J = 15.3, 2H), 3.61 ($^1/_2$ AXq, J = 15.7, 2H), 4.21 (q, J = 7.1, 2H), 7.26 (m, 2H), 7.41 (m, 2H), 7.71 (m, 2H).

Friedel-Crafts Reaction of 1,8-Dimethylnaphthalene. A 20 mL three-necked round-bottomed flask equipped with a magnetic bar and nitrogen inlet and outlet was charged with freshly sublimed $AlCl_3$ (750 mg, 5.62 mmol). Then dry nitrobenzene (4 mL) was introduced, and the mixture was stirred at 20 °C for 5 min. To the resulting greenish yellow reaction mixture, a solution of dimethyl malonyldichloride (375 mg, 2.21 mmol) in dry nitrobenzene (1.5 mL) was added and stirred for another 5 min. Then 1,8-dimethylnaphthalene **14** (300 mg, 1.92 mmol) was added in small portions with the help of a solid addition funnel during a period of $^1/_2$ h, and stirring was continued for 1.5 h. Then the mixture was poured into an ice cold solution of 1 N HCl (30 mL) at 0 °C. After the solution was stirred for 5 min with dichloromethane (30 mL), the layers were separated and the aqueous layer was extracted with dichloromethane. The combined organic layers were washed with water and brine and then dried. The solvent was evaporated, and from the residue excess of nitrobenzene was removed by vacuum distillation. The crude product was chromatographed on a silica gel column by eluting with hexane−ethyl acetate mixture (1:4) to give the first compound **16** 5%. Mp, 120−122 °C. IR (KBr): ν 1730, 1696 cm^{-1}. This was followed by the second isomer **17** (33%, mp, 136−138 °C). IR (KBr): ν 1700, 1666 cm^{-1}. ^1H NMR: δ 1.34 (s, 6H), 3.03 (s, 3H), 3.39 (s, 3H), 7.48−7.56 (m, 2H), 7.89−7.92 (m, 1H), 8.33 (s, 1H). MS: *m*/*e* 252 (M^+). Further elution of the column gave the required symmetrical dione **15** (45%, mp, 105−107 °C). IR (KBr): ν 1697, 1666 cm^{-1}. ^1H NMR: δ 1.48 (s, 6H), 3.52 (s, 6H), 7.51 ($^1/_2$ ABq, J = 7.5, 2H), 8.26 ($^1/_2$ ABq, J = 7.5, 2H). ^{13}C NMR: δ 22.6, 26.8, 57.9, 126.1, 128.5, 130.1, 132.3, 133.0, 143.5, 199.3. MS: *m*/*e* 252 (M^+). Anal. Calcd for $C_{17}H_{16}O_2$: 80.92; H, 6.39. Found: C, 80.93; H, 6.25.

6,7-Bis(bromomethyl)-2,2-dimethyl-1*H*-phenalene-1,3-(2*H*)-dione (10). To a solution of dimethyl phenalene dione derivative **15** (252 mg, 1 mmol) and AIBN (15 mg) in carbon tetrachloride (14 mL) was added *N*-bromosuccinimide (391 mg, 2.2 mmol). The reaction mixture was refluxed for 3 h. Then the flask was cooled in an ice bath and the insoluble succinimide was filtered off. Then the filtrate was concentrated on a rotary evaporator. Crystallization of the crude product from hexane and carbon tetrachloride afforded **10** as light brown crystalline needles in 86% yield. Mp, 175−176 °C. IR (KBr): ν 1701, 1670 cm^{-1}. ^1H NMR: δ 1.51 (s, 6H), 5.29 (s, 4H), 7.86 ($^1/_2$ ABq, J = 7.5, 2H), 8.42 ($^1/_2$ ABq, J = 7.5, 2H). ^{13}C NMR: δ 22.5, 35.2, 58.5, 128.9, 129.1, 133.1, 133.5, 134.0, 140.2, 198.4. MS: *m*/*e* 410 (M^+). Anal. Calcd for $C_{17}H_{14}Br_2O_2$: C, 49.78; H, 3.44. Found: C, 49.64; H, 3.31.

Ethyl 2-Isocyano-1,2,3,6,7,8-hexahydro-7,7-dimethyl-6,8-dioxopyrene-2-carboxylate (24). Prepared from dibromide **10** as a light brown needles in 40% isolated yield. Mp, 172−173 °C. IR (KBr): ν 2140, 1740, 1703 cm^{-1}. UV ($CHCl_3$): λ_{max} nm (ϵ M^{-1} cm^{-1}) 338 (1940), 248 (2190). ^1H NMR: δ 1.33 (t, J = 7.1, 3H), 1.53 (d, J = 2.0, 6H), 3.68 ($^1/_2$ ABq, J = 16.3, 2H), 3.82 ($^1/_2$ ABq, J = 16.6, 2H), 4.38 (q, J = 7.1, 2H), 7.60 (d, J = 7.3, 2H), 8.41 (d, J = 7.5, 2H). ^{13}C NMR: δ 14.0, 22.4, 23.2, 40.1, 58.7, 61.4, 63.6, 126.5, 127.3, 129.0, 131.1, 136.6, 160.2, 167.5, 198.7. MS: *m*/*e* 361 (M^+). Anal. Calcd for $C_{17}H_{15}$-NO_2: C, 73.05; H, 5.29; N, 3.86. Found: C, 72.88; H, 5.16; N, 3.69. **Hydrolysis product:** White solid, 90%. Mp, 180 °C (dec). IR (KBr): ν 3360, 1745, 1700 cm−1. [1] NMR: δ 1.20 (t, J = 7.1, 3H), 1.49 (s, 3H), 1.51 (s, 3H), 1.90 (br s, 2H), 3.35 ($^1/_2$ AXq, J = 16.4, 2H), 3.72 ($^1/_2$ AXq, J = 16.4, 2H), 4.19 (q, J = 7.1, 2H), 7.55 ($^1/_2$ ABq, J = 7.5, 2H), 8.37 ($^1/_2$ ABq, J = 7.3, 2H).

Ethyl 3-Isocyano-2,3-dihydro-4*H*-cyclopenta[*b*]-6,11-anthraquinone-3-carboxylate (25). Prepared from 2,3-bis-(bromomethyl)-1,4-anthraquinone **11** as a yellow crystalline solid in 45% yield. Mp, 207−208 °C. IR (KBr): ν 2138, 1746, 1671 cm^{-1}; UV ($CHCl_3$): λ_{max} nm (ϵ M^{-1} cm^{-1}) 326 (1150), 260 (1810). ^1H NMR: δ 1.38 (t, J = 7.1, 3H), 3.65 ($^1/_2$ ABq, J = 17.0, 2H), 3.84 ($^1/_2$ ABq, J = 17.0, 2H), 4.38 (q, J = 7.1, 2H), 7.82 (dd, J = 5.6, 3.2, 2H), 8.21 (s, 2H), 8.32 (dd, J = 5.6, 3.2, 2H). Anal. Calcd for $C_{21}H_{15}NO_4$: C, 73.03; H, 4.38; N, 4.05. Found: C, 73.18; H, 4.09; N, 4.06. **Hydrolysis product:** Light yellow solid, 66%. Mp, 220−222 °C. IR (neat): ν 3355, 1724, 1670 cm^{-1}. ^1H NMR: δ 1.31 (t, J = 7.1, 3H), 1.65 (br s, 2H), 3.06 ($^1/_2$ AXq, $J = 16.8$, 2H), 3.66 ($^1/_2$ AXq, $J = 16.3$, 2H), 4.25 (q, $J = 7.1$, 2H), 7.78 (m, 2H), 8.16 (s, 2H), 8.3 (m, 2H).

Ethyl 7-Isocyano-6,7-dihydro-8*H*-cyclopenta[*g*]quinoxaline-7-carboxylate (26). Prepared from 2,3-bis(bromomethyl)quinoxaline **12** as a light brown solid in 40% yield. Mp, 110−112 °C. IR (KBr): ν 2137, 1736 cm^{-1}. UV (CHCl$_3$): λ_{max} nm (ϵ M^{-1} cm^{-1}) 323 (81890), 245 (5030). ^{1}H NMR: δ 1.38 (t, $J =$ 7.1, 3H), 3.71 ($^1/_2$ ABq, $J = 16.8$, 2H), 3.90 ($^1/_2$ ABq, $J = 16.8$, 2H), 4.36 (q, $J = 7.1$, 2H), 7.98 (s, 2H), 8.82 (s, 2H). ^{13}C NMR: δ 13.9, 45.6, 63.4, 68.5, 124.7, 141.4, 142.9, 144.6, 159.8, 167.7. MS: *m*/*e* 277 (M$^+$). Anal. Calcd for $C_{15}H_{13}N_3O_2$: C, 67.40; H, 4.90; N, 15.72. Found: C, 67.77; H, 4.83; N, 15.29. **Hydrolysis product:** White solid, 94%. IR (KBr): ν 3357, 1720 cm^{-1}. ^{1}H NMR: δ 1.27 (t, $J = 7.1$, 3H), 1.88 (s, 2H), 3.08 ($^1/_2$ AXq, $J =$ 16.6, 2H), 3.71 ($^1/_2$ AXq, $J = 16.8$, 2H), 4.22 (q, $J = 7.1$, 2H), 7.87 (s, 2H), 8.71 (s, 2H).

Ethyl 4-Isocyano-3,4-dihydro-5*H*-cyclopenta[*c*]furan-4-carboxylate (27). Prepared from 3,4-bis(bromomethyl)furan **13** as a white solid in 67% yield. Mp, 40−42 °C. IR (KBr): ν 2138, 1740 cm^{-1}. ^{1}H NMR: δ 1.35 (t, $J = 7.1$, 3H), 3.22 ($^1/_2$ ABq, $J = 15.9$, 2H), 3.41 ($^1/_2$ ABq, $J = 15.9$, 2H), 4.32 (q, $J =$ 7.1, 2H), 7.18 (s, 2H). ^{13}C NMR: δ 14.0, 37.8, 68.0, 126.8, 134.5, 159.6, 167.9. MS: *m*/*e* 205 (M$^+$). **Hydrolysis product:** Light yellow liquid, 78%. IR (KBr): ν 3367, 1725 cm^{-1}. ^{1}H NMR: δ 1.22 (t, $J = 6.9$, 3H), 2.37 (s, 2H), 2.64 ($^1/_2$ ABq, $J = 16.5$, 2H), 3.17 ($^1/_2$ ABq, $J = 15.9$, 2H), 4.16 (q, $J = 6.9$, 2H), 7.06 (s, 2H).

Diethyl 2,6-Diisocyano-1,2,3,5,6,7-*s*-hexahydroindacene-2,6-dicarboxylate (29a and 29b). Two isomers were formed from 1,2,4,5-tetrakis(bromomethyl)benzene **28** as crystalline solids in 42% combined yield. **Compound 29a:** 21%; mp, 166−168 °C. IR (KBr): ν 2137, 1742 cm^{-1}. UV (CHCl$_3$): λ_{max} nm (ϵ M^{-1} cm^{-1}) 284 (2836), 277 (3390). ^{1}H NMR: δ 1.35 (t, $J = 7.1$, 6H), 3.42 ($^1/_2$ ABq, $J = 15.6$, 4H), 3.66 ($^1/_2$ ABq, $J = 15.7$, 4H), 4.33 (q, $J = 7.1$, 4H), 7.12 (s, 2H). ^{13}C NMR: δ 14.6 (q), 46.4 (t), 63.8 (t), 69.2 (s), 121.6 (d), 138.4 (s), 159.4 (s), 168.9 (s). MS: *m*/*e* 352 (M$^+$). Anal. Calcd for $C_{20}H_{20}N_2O_4$: C, 68.16; H, 5.71; N, 7.95. Found: C, 68.18; H, 5.83; N, 7.79. **Hydrolysis product:** White crystalline solid, 67%. Mp, 91−93 °C. IR (KBr): ν 3348, 1724 cm^{-1}. ^{1}H NMR: δ 1.29 (t, $J = 7.3$, 6H), 1.72 (s, 4H), 2.81 ($^1/_2$ AXq, $J = 15.0$, 4H), 3.48 ($^1/_2$ AXq, $J =$ 15.0, 4H), 4.21 (q, $J = 7.3$, 4H), 7.06 (s, 2H). **Compound 29b:** 21%; mp, 152−154 °C. IR (KBr): ν 2135, 1734 cm^{-1}. UV (CHCl$_3$): λ_{max} nm (ϵ M^{-1} cm^{-1}) 283 (2270), 278 (2300). ^{1}H NMR: δ 1.35 (t, $J = 7.1$, 6H), 3.35 ($^1/_2$ ABq, $J = 15.6$, 4H), 3.67 ($^1/_2$ ABq, $J = 15.7$, 4H), 4.31 (q, $J = 7.1$, 4H), 7.11 (s, 2H). ^{13}C NMR: δ 14.7 (q), 46.4 (t), 63.9 (t), 68.8 (s), 121.5 (d), 138.5 (s), 159.6 (s), 169.1 (s). MS: *m*/*e* 352 (M$^+$). **Hydrolysis product:** White crystalline solid, 64%. Mp, 123−125 °C. IR (KBr): ν 3350, 1725 cm^{-1}. ^{1}H NMR: δ 1.29 (t, $J = 7.1$, 6H), 1.69 (br s, 4H), 2.81 ($^1/_2$ AXq, $J = 15.2$, 4H), 3.52 ($^1/_2$ AXq, $J =$ 15.2, 4H), 4.21 (q, $J = 7.1$, 4H), 7.06 (s, 2H).

Triethyl 2,5,8-Triisocyano-2,5,8-triindantricarboxylate (31 and 32). Prepared from hexakis(bromomethyl)benzene **30**. Two isomers were formed in 1:2 ratio as crystalline solids in 30% combined yield. Major isomer **31** (unsymmetrical): mp, 148−149 °C. IR (KBr): ν 2142, 1729, 1743 cm^{-1}. UV (CHCl$_3$): λ_{max} nm (ϵ M^{-1} cm^{-1}) 360 (680), 234 (1590). ^{1}H NMR: δ 1.36 (t, $J = 7.3$, 6H), 1.37 (t, $J = 7.1$, 3H), 3.32 (m, 6H), 3.63 (t, $J = 15.7$, 6H), 4.34 (q, $J = 7.1$, 4H), 4.36 (q, $J = 7.1$, 2H). ^{13}C NMR: δ 14.0 (2C), 44.6, 44.7 (2C), 63.4 (2C), 68.0, 68.4, 134.0 (3C), 159.2, 159.5, 167.9, 168.1. HRMS: *m*/*e* for $C_{27}H_{27}N_3O_6$ Calcd 489.1899; found 489.1907. **Hydrolysis product:** Colorless liquid, 85%. IR (neat): ν 3350, 1725 cm^{-1}. ^{1}H NMR: δ 1.29 (m, 9H), 1.92, (s, 6H), 2.76 (m, 6H), 3.45 (m, 6H), 4.22 (q, $J = 7.3$, 6H). Minor isomer **32** (symmetrical): mp, 120−121 °C. IR (KBr): ν 2140, 1748 cm^{-1}. UV (CHCl$_3$): λ_{max} nm (ϵ M^{-1} cm^{-1}) 270 (7210), 241 (1720). ^{1}H NMR: δ 1.36 (t, $J = 7.1$, 9H), 3.46 ($^1/_2$ ABq, $J = 15.9$, 6H), 3.59 ($^1/_2$ ABq, $J = 15.7$, 6H), 4.32 (q, $J = 7.1$, 6H). **Hydrolysis product:** Colorless liquid, 80%. IR (neat): ν 3350, 1725 cm^{-1}. ^{1}H NMR: δ 1.29 (t, $J = 6.9$, 9H), 1.98 (s, 6H), 2.75−2.85 (m, 6H), 3.37−3.77 (m, 6H), 4.22 (q, $J = 7.3$, 6H).

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