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Synthesis of Highly Functionalised Dibenzylglycine Derivatives Via the Suzuki–Miyaura Coupling Reaction†

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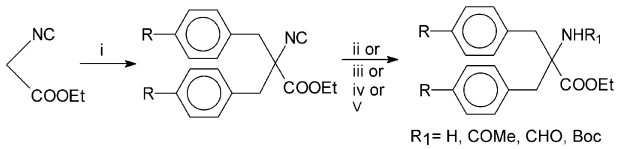
Abstract—Several α,α-dibenzylglycine (α-benzylphenylalanine) derivatives were prepared by alkylation of the ethyl isocyanoacetate with different benzyl bromide derivatives. Various aryl groups were introduced in the dibenzylglycine moiety via the Suzuki–Miyaura coupling reaction.

α,α-Disubstituted amino acids (α,αAAs) are important members of modified amino acids.[1] Replacement of the α-hydrogens of glycine by an alkyl group leads to α,αAAs. The steric hindrance of the quaternary centre of the α-aminoisobutyric acid (Aib) combined with helix forming capacity of this amino acid has attracted the attention of structural biologists and protein crystallographers.[2] The dibenzylglycine (Dbzg) is a special structural variant of Aib. In recent years, there has been an increasing interest in the synthesis of structural variants of Aib with the aim of incorporating them into peptides instead of Aib. The presence of two benzyl groups at α position of Dbzg not only provides rigidity to the peptide backbone in which it is incorporated, but also acts as a useful vehicle for studying π–π interactions.[3,4] In this context, a general approach for the synthesis of Dbzg derivatives is of immense importance.

A perusal of literature revealed that the preparation of Dbzg is not a trivial exercise. For example, preparation of the Dbzg by the Bucherer–Berg method,[5] or the Ugi three-component procedure[6] or the Schmidt rearrangement method[7] is limited to only simple substitution pattern. The dibenzyl hydantoin prepared by the Bucherer–Berg method have been difficult to hydrolyse to the free amino acid under drastic reaction conditions due to steric hindrance.[8] A more recent method involving alkylation of the ketimine derivative with benzyl bromides require 5 equivalents of alkyl halide and 10 equivalents of base.[9] Although this method is suitable for commercially available and inexpensive bromides, it is not suitable for the preparation of highly functionalised substrates. Surprisingly, in some instances even glycine-based chiral auxiliaries[10] have been used to prepare achiral Dbzg derivatives, as there are no simple glycine equivalents available which can undergo dialkylation with benzyl bromides.

Herein, we describe for the first time a general and useful method for the preparation of a variety of Dbzg derivatives using the ethyl isocyanoacetate as a glycine equivalent.[11] We have also shown that these α,αAA derivatives can further be modified by the Suzuki–Miyaura[12] coupling reaction as a key step. To test this idea, several glycine equivalents were screened for dibenzylation and found that the reaction of benzyl bromides with ethyl isocyanoacetate in NaH/DMSO conditions[13] gave a mixture of both the mono- and dialkylated products. In this regard, alkylation of various glycine equivalents under phase-transfer catalysis (PTC) conditions was investigated.[14,15] We found that under PTC conditions [tetrabutylammonium hydrogensulfate (TBAHS), K_2CO_3, CH_3CN, reflux] the ethyl isocyanoacetate can be dibenzylated in high yield. Having found the suitable conditions for the dialkylation with various benzyl bromide derivatives (Scheme 1), the



Scheme 1. (i) Benzyl bromide, PTC, K_2CO_3; (ii) concd HCl, EtOH; (iii) Ac_2O, DMAP; (iv) concd HCl, diethyl ether; (v) Boc_2O, chloroform.

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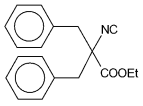
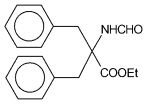
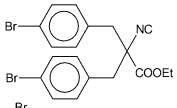
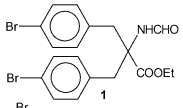
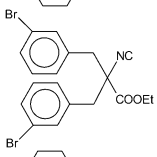
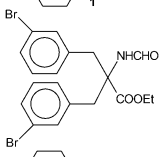
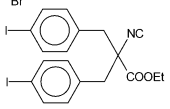
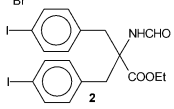
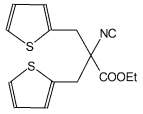
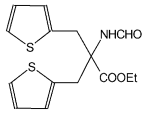
Table 1. List of various derivatives prepared under PTC conditions

S no.	Dialkylated product	Yield (%)	Hydrolysis product	Yield (%)	Mp (°C)
1		88		72	163–165
2		70		98	104–106
3		70		59	110–112
4		32		71	158–160
5		33		66	138–140

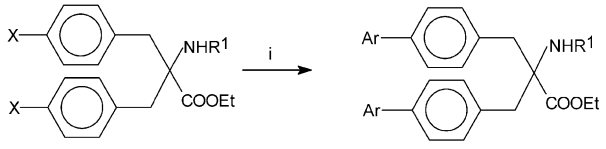
attention was then directed towards the hydrolysis of the isonitrile moiety to generate various amino ester derivatives of Dbzg. In this regard, isonitrile derivative was treated with concd HCl in ethanol to give an amino ester along with *N*-formyl derivative.[16] Attempts to separate the amino compound from *N*-formyl derivative by acid-base work up procedure was ineffective. Consequently, the total hydrolysis mixture was treated with acetic anhydride in the presence of 4-(dimethylamino)-pyridine. After standard workup, we were unable to separate the acetyl and formyl derivatives by silica gel column chromatography. Therefore, the isonitrile derivative was treated with concd HCl in ether to deliver the *N*-formyl derivative as the sole product and thus avoiding the separation of the contaminated acetyl derivative. Various formyl derivatives prepared by this procedure are shown in Table 1. The required benzyl bromides are either commercially available or prepared by tactical adoption of the known procedures.[17]

Having prepared various dibenzylglycine derivatives, the attention was then focused on the Suzuki–Miyaura coupling of the dibromo derivative **1**. Attempts to couple **1** with various boronic acid derivatives under Pd(0) catalysis conditions proved to be ineffective (Scheme 2). Although, various ligands are known to catalyse the unreactive arenes for Suzuki–Miyaura coupling,[18] the diiodo compound **2** was chosen as the starting substrate to test the Suzuki–Miyaura reaction. In this regard, the coupling reaction of the diiodo compound **2** with various boronic acids was attempted and the cross-coupling products were obtained in good yield (Table 2). Since *N*-Boc derivatives are useful in peptide synthesis we have prepared *N*-Boc protected derivative **3** and performed the coupling reaction. The cross-coupling products reported in Tables 2 and 3 shows that this approach is more versatile than the direct alkylation method. Moreover, preparation of the building block **2** allows the synthesis of highly substituted Dbzg derivatives easily.

In summary, the methodology developed here increase the scope of the application of ethyl isocyanoacetate as a glycine equivalent. Since incorporation of α,αAA into peptides lead to modified analogues with increased lipophilicity and increased resistance to enzymatic hydrolysis, the methodology developed here is likely to find useful applications in bioorganic and medicinal chemistry. The strategy adopted here for the generation of various Dbzg derivatives via the Suzuki–Miyuara coupling reaction may be useful for the development of lead modification in peptide drugs by a combinatorial approach.

General Procedure for Alkylation of Ethyl Isocyanoacetate with Various Benzyl Bromides

To a solution of the ethyl isocyanoacetate (0.5 mmol) in acetonitrile (12 mL) was added finely powdered K_2CO_3 (6 mmol) and TBAHS (0.3 mmol) and the electrophile (1 mmol). The resulting heterogeneous mixture was heated at 70–80 °C for 12–20 h (or stirred at rt in case of



1: X = Br, R^1=CHO
2: X=I, R^1=CHO
3: X=I, R^1=Boc

Scheme 2. (i) $ArB(OH)_2$, Pd(0), Na_2CO_3, THF/toluene, H_2O.

Table 2. List of various *N*-formyl derivatives of dibenzylglycines prepared by Suzuki–Miyaura coupling reaction

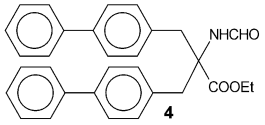
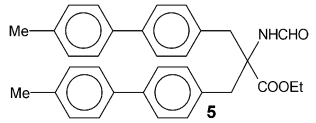
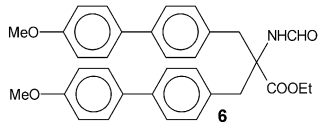
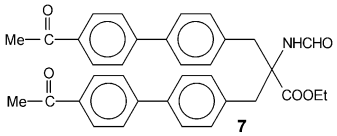
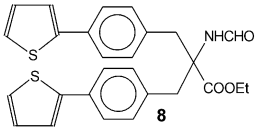
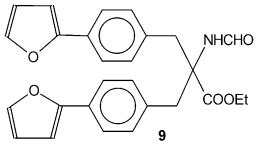
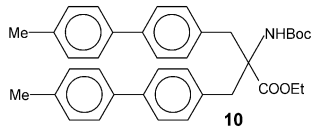
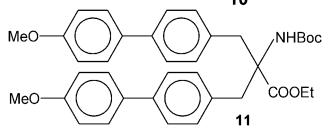
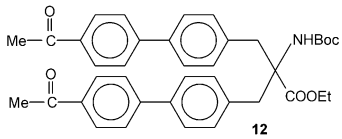
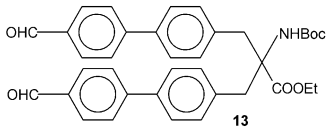
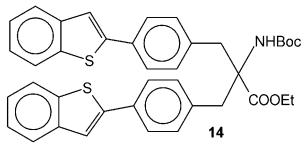
S no.	Cross-coupling product	Yield (%)	Mp (°C)
1	 4	72	145–147
2	 5	81	151–153
3	 6	86	176–178
4	 7	70	216–218
5	 8	93	124–126
6	 9	92	130–132

Table 3. List of various *N*-Boc derivatives of dibenzylglycines prepared by Suzuki–Miyaura coupling reaction

S no.	Cross-coupling product	Yield (%)	Mp (°C)
1	 10	72	172–73
2	 11	96	—
3	 12	72	62–64
4	 13	53	150–52
5	 14	79	142–44

thiophene) until all the starting material 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. The residue was taken in diethyl ether and washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the material was purified by silica gel column chromatography. Elution of the column with ethyl acetate/pet ether mixture gave the isonitrile derivative.

General Procedure for the Hydrolysis of the Coupling Product

A solution of the coupling product (1 mmol) in diethyl ether (5–10 mL) was added a few drops of concentrated HCl at 0 °C and the reaction mixture was stirred at rt. At the end of the reaction (TLC monitoring), water (4–6 mL) was added and the reaction mixture was extracted with diethyl ether and washed with water, brine and dried over $MgSO_4$. Then the solvent was evaporated at reduced pressure and the product was purified by silica gel column chromatography. Elution of the column with ethyl acetate/pet ether mixture gave the required *N*-formyl derivative.

General Procedure for Suzuki Coupling Reactions

To the solution of **2** (1 equiv) in THF/toluene (1:1), aryl boronic acid (4 equiv) and Na_2CO_3 (4 equiv) in H_2O was added. Then, the reaction mixture was degassed for 30 min and $Pd(PPh_3)_4$ (10 mol%) was added. The resultant mixture was heated to (70–80 °C) for several hours until all the starting material has been consumed (TLC monitoring). The reaction mixture was cooled to rt and extracted with dichloromethane, washed with water, brine and dried over $MgSO_4$. The solvent was evaporated and the product was purified by silica gel column chromatography. Elution of the column with ethyl acetate/pet ether mixture gave the cross-coupling product.[19]

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19. Selected ^{1}H NMR ($CDCl_3$, 300 MHz) data for cross-coupling products. **4**: δ 1.43 (t, J = 6.9 Hz, 3H), 3.37 (d, J = 13.5 Hz, 2H), 4.04 (d, J = 13.5 Hz, 2H), 4.28 (q, J = 6.9 Hz, 2H), 6.29 (s, 1H), 7.17–7.57 (m, 18H), 8.25 (s, 1H); **5**: δ 1.42 (t, J = 7.1 Hz, 3H), 2.38 (s, 6H), 3.35 (d, J = 13.5 Hz, 2H), 4.02 (d, J = 13.5 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 6.28 (s, 1H), 7.15–7.24 (m, 8H), 7.44–7.47 (m, 8H), 8.24 (s, 1H); **6**: δ 1.43 (t, J = 7.3 Hz, 3H), 3.35 (d, J = 13.5 Hz, 2H), 3.84 (s, 6H), 4.01 (d, J = 13.5 Hz, 2H), 4.28 (q, J = 7.3 Hz, 2H), 6.28 (s, 1H), 6.94–6.98 (m, 4H), 7.14–7.21 (m, 4H), 7.42–7.70 (m, 8H), 8.24 (s, 1H); **7**: δ 1.45 (t, J = 7.1 Hz, 3H), 2.63 (s, 6H), 3.38 (d, J = 13.7 Hz, 2H), 4.06 (d, J = 13.7 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 6.28 (s, 1H), 7.21 (d, J = 8.1 Hz, 4H), 7.52 (d, J = 8.1 Hz, 4H), 7.65 (d, J = 8.4 Hz, 4H), 8.0 (d, J = 8.4 Hz, 4H), 8.1 (s, 1H); **8**: δ 1.42 (t, J = 7.1 Hz, 3H), 3.32 (d, J = 13.5 Hz, 2H), 3.99 (d, J = 13.5 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 6.25 (s, 1H), 7.01–7.13 (m, 6H), 7.24–7.27 (m, 4H), 7.48–7.51 (m, 4H), 8.2 (s, 1H); **9**: δ 1.40 (t, J = 7.3 Hz, 3H), 3.3 (d, J = 13.5 Hz, 2H), 3.98 (d, J = 13.5 Hz, 2H), 4.24 (q, J = 7.3 Hz, 2H), 6.23 (s, 1H), 6.44 (dd, J = 3.4, 3.2 Hz, 2H), 6.59 (dd, J = 3.4, 3.2, 2H), 7.12 (d, J = 6.5 Hz, 4H), 7.43 (dd, J = 1.8, 1.8 Hz, 2H), 7.55 (d, J = 6.5 Hz, 4H), 8.2 (s, 1H); **10**: δ 1.34 (t, J = 6.96 Hz, 3H), 1.53 (s, 9H), 2.38 (s, 6H), 3.2 (d, J = 13.1 Hz, 2H), 3.8 (d, J = 13.1 Hz, 2H), 4.2 (q, J = 6.96 Hz, 2H), 5.37 (s, 1H), 7.14–7.25 (m, 8H), 7.45–7.47 (m, 8H); **11**: δ 1.37 (t, J = 7.2 Hz, 3H), 1.55 (s, 9H), 3.25 (d, J = 13.2 Hz, 2H), 3.85 (s, 6H), 3.9 (d, J = 13.2 Hz, 2H), 4.2 (q, J = 7.2 Hz, 2H), 5.3 (s, 1H), 6.9 (d, J = 8.4 Hz, 4H), 7.1 (d, J = 8.4 Hz, 4H), 7.4 (d, J = 8.4 Hz, 4H), 7.5 (d, J = 8.4 Hz, 4H); **12**: δ 1.36 (t, J = 6 Hz, 3H), 1.55 (s, 9H), 2.64 (s, 6H), 3.2 (d, J = 12 Hz, 2H), 3.9 (d, J = 12 Hz, 2H), 4.2 (q, J = 6 Hz, 2H), 5.3 (s, 1H), 7.2 (d, J = 9 Hz, 4H), 7.5 (d, J = 9 Hz, 4H), 7.6 (d, J = 9 Hz, 4H), 8.0 (d, J = 9 Hz, 4H); **13**: δ 1.38 (t, J = 6.9 Hz, 3H), 1.55 (s, 9H), 3.2 (d, J = 13.3 Hz, 2H), 3.9 (d, J = 13.3 Hz, 2H), 4.2 (q, J = 6.9 Hz, 2H), 5.3 (s, 1H), 7.1 (d, J = 8.1 Hz, 4H), 7.5 (d, J = 8.1 Hz, 4H), 7.7 (d, J = 8.1 Hz, 4H), 7.9 (d, J = 8.1 Hz, 4H), 10.0 (s, 2H); **14**: δ 1.3 (t, J = 7.5 Hz, 3H), 1.5 (s, 9H), 3.2 (d, J = 13.3 Hz, 2H), 3.9 (d, J = 13.3 Hz, 2H), 4.2 (q, J = 7.5 Hz, 2H), 5.3 (s, 1H), 7.1–7.9 (m, 8H), 7.45–7.47 (m, 10H).