

2,2-Bis(ethoxycarbonyl)vinyl (BECV) as a Versatile Amine Protecting Group for Selective Functional-Group Transformations

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Dedicated to Professor Masataka Ihara for his contributions to organic synthesis

Abstract: A 2,2-Bis(ethoxycarbonyl)vinyl- (BECV) group was used for the selective protection of amines at room temperature in the presence of potentially interfering functional groups such as OH, SH, COOH as well as other NH₂ groups. Several functional group transformations such as esterification, O-alkylation, O-acylation, N-alkyla-

tion, N-acylation, S-alkylation can selectively be carried out in the presence of the BECV group. The selective deprotection of the BECV group was

Keywords: amines • amino acids • deprotection • functional-group transformations • protecting groups

achieved in a short time using ethylenediamine at room temperature while several other functional groups such as benzoate, aliphatic esters, amides and ethers remain intact. The BECV group shows orthogonal stability against the common protecting groups such as Fmoc, Cbz and Boc.

Introduction

The carbamate derivatives occupy a prominent position in the ranks of commonly used amine protecting groups (PGs). The advantage of carbamate PGs, such as Boc, Cbz, Fmoc and its recent variants Alloc, Troc and Azoc^[1] over other amine PGs is that the cleavage condition can be varied considerably, depending on the choice of alkyl component used. These PGs are useful for the synthesis of peptides, aminoglycosides and functionalized aromatic amines. However, some of the reagents used for the carbamate protection such as Fmoc-Cl are expensive and moisture-sensitive.^[2] Moreover, these reagents are CO₂- and COCl₂-based chemicals^[3] are difficult to prepare as special precaution is needed for preparation even on the industrial scale. Despite these drawbacks, the use of carbamate PGs is being continued, due to a lack of alternative PGs that meet the required standards.^[2] Hence, there is a clear need to develop alternative amine protecting groups.

The primary amine protecting group, 1-(4,4-dimethyl-2,6-dioxocyclohexylidene)ethyl (Dde),^[4] introduced as an alternative to carbamates, has become a valuable tool for the construction of cyclic side-chain modified peptides and peptide nucleic acid-peptide conjugates.^[5] The Dde group is fully orthogonal to the Fmoc protecting group.^[6] Later, some of its variants were introduced to overcome its drawbacks such as intramolecular *N-N'*-migration,^[5,6] stability towards Fmoc deprotection conditions^[7] and lack of fluorescence emission.^[8] The types of reactions carried out using the Dde-protected amines are only limited. These include amide or carbamate bond formation in peptides and polyamines,^[9] reactions involving the use of mild reagents such as tertiary amine, secondary amine, inorganic base (Cs₂CO₃),^[7] and 1 % TFA. The reason for this limited study may be due to the presence of sterically hindered but acidic protons in the 1,3-cyclohexanedione ring system of the Dde group which may lead to side reactions if strong bases such as NaH, LDA, NaOH are used. Another reason as observed by Bycroft et al. is that the development of Dde was to a large extent influenced by the availability of dimedone and its conversion to 2-acetyl-5,5-dimethylcyclohexane-1,3-dione by acylation reaction.^[10] We found that the 2,2-bis(ethoxycarbonyl)vinyl- (BECV) group, an ester-type variant of Dde, met some of the essential requirements for an amine protection group, which we describe herein.

In the course of our attempt to synthesize novel heterocycles we observed a facile deprotection of the BECV group

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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.200902054>.

on **1a** in the presence of ethylenediamine in ethanol to give product **1** in quantitative yield (99%) at room temperature (Table 1). The use of readily available organic reagent ethylenediamine, simple reaction conditions and the high yield of the deprotected product provided the scope for further development of the synthesis. A complete literature review revealed that the BECV group was used as an amine PG in the synthesis of amino acid esters^[11] and aminoglycosides.^[12] However, no further reports were made mainly because the amine protection requires the use of strong base KOH and the deprotection involves the use of harmful reagents, such as 4% solutions of Br₂ or Cl₂ in CHCl₃ (wet). The reaction times are usually long (12 h at 40 °C). Side reactions were observed for compounds containing unsaturated bonds, acid-sensitive functional groups, easily oxidizable groups, which led to the formation of carbon-to-nitrogen migration and complex mixture of unidentified products. Further, there was no study on the use of BECV group for selective functional group transformations on different class of organic compounds. This encouraged us to undertake a complete study on the use of BECV as a protecting group. In order to standardize the reaction condition, we examined different solvents, reaction temperature and the use of other amines as deprotecting agents. With the use of less than 4 equiv of ethylenediamine in ethanol, the deprotection reaction is very slow (> 24 h).^[13] By comparing the reaction times of various solvents CHCl₃ (1.5 h), CH₃CN (20 min), H₂O (> 24 h) studied, EtOH (20 min) was found to be suitable in terms of quick reaction time and ecofriendliness. With NH₃, the reaction was very slow (> 24 h),^[14] whereas it was fast with H₂N-NH₂ (5 min),^[15] and no reaction was observed with 1,2-diaminobenzene (> 2 h). However, the use of H₂N-NH₂ may create conditions that are too harsh for selective functional group transformations. We therefore decided to use the more moderate reagent, 4 equiv ethylenediamine in ethanol for our studies.

According to the literature, the BECV group may typically be introduced to amines by heating a neat mixture of an amine and diethyl ethoxymethylenemalonate (DEMM) between 100–120 °C,^[16] or in some cases heating to reflux in ethanol.^[17,18] However, we observed that, the coupling reaction of the BECV group with a variety of aromatic, aliphatic amines takes place with one equivalent of DEMM simply by stirring in ethanol at room temperature. In the case of amino acids, the use of NEt₃ (1 equiv) was sufficient to introduce the BECV group to amine at room temperature. The starting material, DEEM, can be easily synthesized in the laboratory following a simple procedure reported in literature.^[19]

Results and Discussion

In order to investigate the electronic influence of the aromatic ring substituents on protection and deprotection, we used anilines **1–7** (Table 1). The BECV group was introduced in presence of ethanol at room temperature to afford

Table 1. Electronic effect of aromatic substituents on protection/deprotection.

Entry	R	Protection <i>t</i>	Yield [%]	Deprotection <i>t</i>	Yield [%]
1		15 min	99	20 min	99
2		20 min	98	30 min	95
3		5.00 h	99	2 h 15 min	90
4		6.00 h	95	2.5 h	95
5		6.00 h	98	5.0 h	95
6		6.00 h	95	1.5 h	95
7		7.00 h	92	6.0 h	90

an excellent yield of products **1a–7a**. The higher the electron-withdrawing strength of the substituent in the aromatic ring, the slower the rate of coupling. In general, compounds that undergo the coupling reaction slowly are also characterized by slow deprotection. Both protection and deprotection occurred under these conditions in excellent yield. The presence of highly UV-active chromophore in BECV group is an added advantage for monitoring the reaction by TLC.

Multifunctional anilines are useful starting materials for the synthesis of important heterocycles.^[20] In many instances, functional groups, such as OH, SH, COOH and also NH₂, must be selectively manipulated over an amine group. We investigated the compatibility of the BECV group with several potentially competing functional groups (Table 2). In our study, the starting materials **8a–14a** were prepared in very good yields. Except for **8a**, in which two BECV groups were introduced, the yields are excellent and the reaction time was short. This clearly shows that anilines can be protected selectively while the competing functional groups NH₂, OH, SH, and COOH can be left unprotected.

The selectively protected anilines were then subjected to functional group transformations. Acylation and alkylation carried out separately on substrate **8a**, yielded **8c**, **8e** and **8g**. Upon selective deprotection of the BECV group, high yields of **8d**, **8f** and **8g** were obtained very quickly, after 1.5 h, 15 min and 15 min, respectively. Substrate **9a** with a sterically encumbered *ortho*-amino-substituent also behaved in a similar way, demonstrating that one amino group may

Table 2. Selective protection/functional group transformation (FGT)/deprotection of multifunctional aromatic amines.^[a]

Reaction scheme: A multifunctional aromatic amine (A) with a functional group (FG) and a BECV group reacts with ethyl 2-oxo-2-phenylacetate under selective protection conditions (EtOH/RT) to form a protected intermediate. This intermediate then undergoes selective FGT ([b]–[h]/RT) to form a substituted aniline intermediate. Finally, treatment with ethylenediamine (B) in EtOH/RT yields the final substituted aniline product (SFGT).

Entry	Selective protection Starting material	Product	t (Yield [%])	Selective functional group transformation Product	t (Yield [%])	Selective deprotection Product	t (Yield [%]) ^[b]
1			5 min (17)		1.5 h (80) ^[b]		1.5 h (80)
			(77)		24.0 h (78) ^[c]		15 min (99)
2					24.0 h (20) ^[b]		15 min (99)
3			10 min (98)		24 h (77) ^[c]		15 min (99)
4			15 min (99)		3.0 h (85) ^[d]		1.5 h (90)
5					12.0 h (92) ^[e]		1.5 h (95)
6					30 min (99) ^[b]		5 min (95)
7					1.0 h (99) ^[f]		1.0 h (75)
8			15 min (99)		12.0 h (99) ^[c]		15 min (99)
9			20 min (98)		24.0 h (85) ^[c]		2.0 h (98)
10			4.5 h (99)		36.0 h (85) ^[g]		2.0 h (90)
11					2.0 h (98) ^[h]		2 h 151 min (95)
12			5.0 h (98)		2.0 h (98) ^[h]		2.5 h (96)

[a] R = -CH=C(COOCH₂CH₃)₂ = BECV; FGT = Functional group transformations. Reaction conditions [b]–[i]: [b] N(C₂H₅)₃, CHCl₃, CH₃COCl; [c] K₂CO₃, acetone, C₂H₅Br; [d] KOH, acetone, allyl bromide; [e] K₂CO₃, CHCl₃, benzyl bromide; [f] N(C₂H₅)₃, CHCl₃, benzoyl chloride; [g] K₂CO₃, acetone, allyl bromide; [h] K₂CO₃, acetone, methyl iodide; [i] ethanol, ethylenediamine, RT.

be selectively functionalized over another in very high yield. The hydroxyl group in **10a** was alkylated, using allyl bromide and benzyl bromide and esterified using benzoyl chloride and acetyl chloride, thus obtaining **10b**, **10d**, **10f** and **10g**, respectively. The BECV group was deprotected under standard conditions to obtain high yields of the corresponding anilines **10c**, **10e**, and **10h** after a short reaction time. This shows that the OH group can be selectively functional-

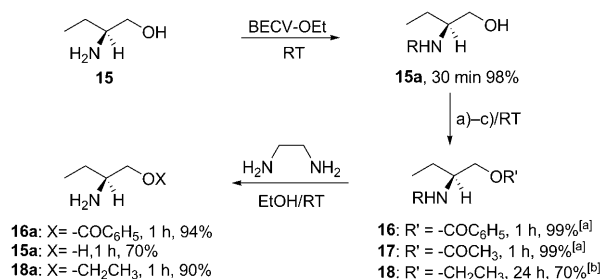
ized to a substituted aniline. However, in the case of compound **10f**, the ethylenediamine deprotected the Ac group instead of the BECV group. The same result was observed even with the milder reagent such as aq. NH₃. Similar is the case with 2-aminophenol (**11**).

Following the same strategy, 2-aminothiophenol (**12**) can be selectively alkylated at the thiol using ethyl bromide to obtain a very good yield of 2-aminothiophenol ethyl ether

(**12c**). Similarly, the 4-aminobenzoic acid derivative **13a** was selectively esterified with allyl bromide and methyl iodide to obtain **13b** and **13d** in excellent yields. On deprotection, compounds **13c** and **13e** were obtained, in which the allyl and alkyl ester remained unaffected. A similar observation was also made using 2-aminobenzoic acid (**14**). This serves as a method for the selective functionalization of the SH and COOH groups in the presence of NH₂ under very mild conditions.

A number of heterocyclizations can be envisaged from several of the bifunctional molecules discussed. However, these heterocyclization reactions require very high temperature. For example, in the synthesis of 7-chloro-6-fluoro-1*H*-quinolin-4-one, a crucial intermediate for the drug norfloxacin^[21] and bipyridine,^[22] the heterocyclization was carried out at <200°C. We did not observe any of the cyclized products under our experimental conditions. All substrates show very good stability at room temperature and under light.

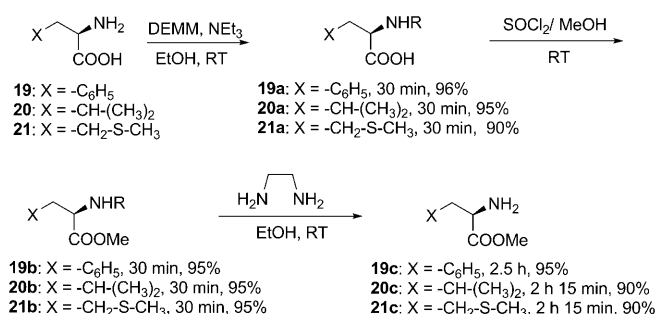
We then checked the versatility of this PG strategy on aliphatic amines. Benzylamine reacted instantly and quantitatively to yield 2-(benzylaminomethylene)malonic acid diethyl ester. The deprotection was completed after 45 min yielding benzylamine (98%). In order to study selective functional group transformation on aliphatic amines (Scheme 1), we



Scheme 1. Aliphatic amines functional group transformations. a) N-(C₂H₅)₃, CHCl₃, C₆H₅COCl; b) N(C₂H₅)₃, CHCl₃, CH₃COCl; c) NaH, C₂H₅Br.

used 2-aminobutanol (**15**). Following treatment with DEMM the selective protection of NH₂ group in the presence of free OH produced very high yields of **15a**. On treatment with acetyl chloride/NEt₃, benzoyl chloride/NEt₃ and ethyl bromide/NaH in separate experiments, compound **15a** yielded the corresponding esters **16** and **17** and ether **18**. These compounds on selective deprotection at room temperature gave the OH-functionalized amines **16a** and **18a** in excellent yields. In a similar manner to phenyl acetate (**10f**), its aliphatic equivalent **17** also underwent acetyl deprotection to yield the starting material **15a**. The hydroxyl group of aliphatic amino alcohols can thus be selectively functionalized. When compared with deprotection aromatic ester **14b**, this result shows that while esters of aromatic acids can survive, esters of aliphatic acid are not stable under the present deprotection condition. All compounds remained optically active.

A crucial test for any amine protecting group is its applicability to amino acid-related functional group transformation.^[23] With this in mind, we investigated the compatibility of the BECV group with amino acid esterification. Protection of the amine group in amino acids (**19–21**) could be carried out at room temperature in the presence of NEt₃ as a base to achieve good yields of **19a–21a** (Scheme 2). Further treatment with SOCl₂/CH₃OH provided excellent yields of the corresponding methyl esters **19b–21b**. The BECV group was tolerant to the reagent SOCl₂/CH₃OH. The deprotection as usual gave amino acid esters **19c–21c** in excellent yields. Optical rotation values were recorded for all compounds and compared with the reported values,^[11] which confirmed that the deprotection conditions do not affect the chiral center.

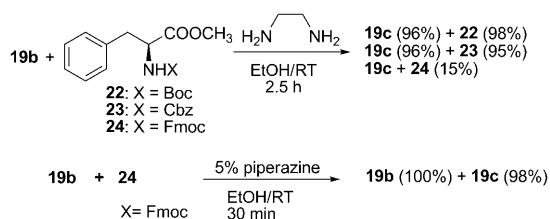


Scheme 2. Amino acid ester preparations.

The main purpose of the amine PG is to suppress its nucleophilic character, primarily by delocalization of the lone pair of electrons.^[3] It is important to note that after the introduction of the BECV group, the aniline or aliphatic amine still possess an NH proton but did not undergo acylation or alkylation even with highly active reagents such as ethyl bromide/NaH, benzyl bromide/K₂CO₃ and acetyl chloride/NEt₃. Thus, we strongly believe that the BECV group can effectively mask the nucleophilic behavior of nitrogen lone pair. In the ¹H NMR spectra of the NH-BECV protected aniline, the peaks corresponding to BECV group were observed at approximate δ values $\cong$ 1.33, 4.33, 8.45, 11.00 ppm. These characteristic peaks do not interfere with the spectral interpretation.

We also studied the orthogonal stability of the BECV group using the common amine protecting groups Boc, Cbz, and Fmoc, as shown in Scheme 3.

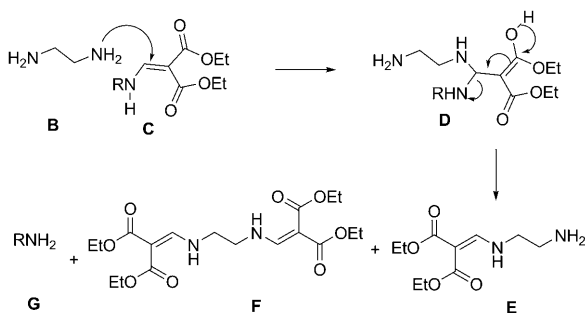
A mixture of NH-BECV protected phenylalanine (**19b**) and compounds **22** or **23** or **24** were separately treated with ethylenediamine (4 equiv) in ethanol. While Boc and Cbz were remained stable, Fmoc was labile. However, when **19b** was treated with 4 equiv of piperazine in ethanol as the deprotection reagent the Fmoc group was exclusively removed without affecting the BECV group. This clearly establishes that the BECV group shows orthogonal stability against Fmoc, Cbz and Boc protecting groups.



Scheme 3. Orthogonal stability of BECV group.

In order to check the stability of BECV group towards basic and acidic conditions,^[5] compounds **19b–21b** were treated with 10% TFA in CH_2Cl_2 , 10% aq. HCl and 20% piperazine in DMF separately at room temperature. All compounds displayed excellent acid/base stability for more than 24 h. In addition as discussed above, the BECV was also stable towards bases such as NaH, KOH, K_2CO_3 , NEt_3 . This implies that the NH-BECV group is adaptable to reaction conditions involving both strong acids as well as base.

After deprotection we were able to isolate mono-BECV (**E**) as well as di-BECV (**F**) protected ethylenediamine (Scheme 4), in addition to free aniline (**G**). Based on this we propose the following mechanism (Scheme 4) for deprotection reaction. We have also observed that, when mono-BECV protected ethylenediamine (**E**) was left at room temperature for longer time, it was converted into di-BECV protected ethylenediamine (**F**) and free ethylenediamine (**B**).



Scheme 4. Mechanism for deprotection.

Conclusion

In summary, we have developed a simple method for the selective protection of amino group as NH-BECV and deprotection of the BECV group, at room temperature, on various substrates such as anilines, aliphatic amines and amino acids. This method is useful for selective functional group transformations of the OH, NH_2 , SH and COOH groups in the presence of the NH_2 group. The BECV protecting group is stable towards both strong acids as well as strong bases except primary amine. The reagents DEMM and ethylenediamine, used for protection and deprotection, respectively, are readily available at much cheaper price compared with

the reagents required for the preparation of carbamate derivatives or Dde protecting group. This study establishes BECV as a versatile amine protecting group that makes use of component materials that are readily available, selectively protect and deprotect under mild conditions and is stable under delicate functional group transformations of varied applications in organic synthesis. In view of these advantages the BECV group could be used as an amine protecting group in line with the well established Dde, Fmoc, Cbz, and Boc protecting groups. Further studies, especially on the application of BECV group to peptide synthesis in solid-phase organic synthesis are currently in progress in our research group.

Experimental Section

General procedure for the protection of amine with BECV group: To a solution of aniline or amine (1 equiv) in ethanol (5% w/v) diethyl ethoxymethylenemalonate (1 equiv) was added and stirred at room temperature ($\sim 28^\circ\text{C}$). After the reaction had been completed, ethanol was evaporated from the reaction mixture under reduced pressure to obtain the corresponding BECV protected aniline or amine in 77–99% yield.

General procedure for the deprotection of BECV group using ethylenediamine: To a solution of BECV protected aniline or amine (1 equiv) in ethanol (5% w/v), ethylenediamine (4 equiv) was added and stirred at room temperature. After the completion of reaction, water was added, extracted with ethyl acetate ($3 \times (5\% \text{ w/v})$). The combined organic layer was dried (Na_2SO_4), evaporated under reduced pressure and passed through a short column (silica gel, hexane/EtOAc) to obtain the corresponding aniline or amine in 75–99% yield.

2-[(4-Hydroxyphenylamino)methylene]malonic acid diethyl ester (10a**):** To a solution of 4-aminophenol (**10**, 0.500 g, 4.5 mmol) in ethanol (2.5 mL), diethyl ethoxymethylenemalonate (925 μL , 4.5 mmol) was added and stirred at room temperature for 15 min. The ethanol in reaction mixture was evaporated under reduced pressure. The title compound was obtained as a white solid (1.26 g, 99%). M.p. 129°C ; ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): $\delta = 1.22\text{--}1.28$ (m, 6H), 4.09–4.22 (m, 4H), 6.80 (d, $J = 8.8$ Hz, 2H), 7.18 (d, $J = 8.8$ Hz, 2H), 8.30 (d, $J = 14.0$ Hz, 1H), 9.47 (s, 1H), 10.70 ppm (d, $J = 14.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 14.2$, 14.3, 60.3, 60.3, 91.7, 116.5, 119.0, 131.9, 153.0, 154.4, 166.6, 169.0 ppm; IR (KBr): $\tilde{\nu} = 710$, 767, 803, 834, 869, 1010, 1031, 1092, 1218, 1354, 1379, 1415, 1463, 1517, 1591, 1622, 1657, 2520, 2619, 2744, 2876, 2933, 2982, 3036, 3200 cm^{-1} ; LCMS (TOF): calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_5$: 279.29; found: 280.2 [$M+H$]; elemental analysis calcd (%) for $\text{C}_{14}\text{H}_{17}\text{NO}_5$: C 60.21, H 6.14, N 5.02; found: C 60.45, H 5.98, N 5.12.

2-[(4-Allyloxyphenylamino)methylene]malonic acid diethyl ester (10b**):** A mixture of **10a** (0.500 g, 1.7 mmol), KOH (0.150 g, 2.6 mmol) in acetone (5 mL) was stirred at room temperature for 30 min. Allyl bromide (232 μL , 2.6 mmol) was added and stirred at room temperature for 3 h. Water (10 mL) was added and extracted with ethyl acetate ($3 \times 10\text{ mL}$). The combined organic layer was washed with water (5 mL), dried (Na_2SO_4) and evaporated under reduced pressure. Title compound was obtained as a white solid (0.48 g, 85%) after passing the crude product through column chromatography (silica gel, hexane/EtOAc 8:2). M.p. 48°C ; ^1H NMR (400 MHz, CDCl_3): $\delta = 1.28\text{--}1.37$ (m, 6H), 4.19–4.31 (m, 4H), 4.52 (t, $J = 4.8$ Hz, 2H), 5.27 (d, $J = 10.4$ Hz, 1H), 5.39 (d, $J = 17.2$ Hz, 1H), 5.97–6.07 (m, 1H), 6.90 (d, $J = 8.8$ Hz, 2H), 7.05 (d, $J = 8.8$ Hz, 2H), 8.41 (d, $J = 14.0$ Hz, 1H), 10.96 ppm (d, $J = 14.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 14.2$, 14.3, 59.8, 60.1, 92.4, 115.7, 117.7, 118.6, 132.7, 132.8, 152.4, 156.0, 165.7, 169.0 ppm; IR (KBr): $\tilde{\nu} = 516$, 555, 758, 792, 945, 991, 1026, 1091, 1175, 1229, 1309, 1386, 1414, 1442, 1473, 1514, 1607, 1680, 2904, 2981, 3252 cm^{-1} ; elemental analysis calcd (%) for $\text{C}_{17}\text{H}_{21}\text{NO}_5$: C 63.94, H 6.63, N 4.39; found: C 63.82, H 6.55, N 4.41.

4-Allyloxyphenylamine (10c): To a solution of BECV-protected aniline (**10b**, 0.500 g, 1.5 mmol) in ethanol (2.5 mL), ethylenediamine (418 μ L, 6.2 mmol) was added at room temperature and stirred for 1.5 h. After the completion of reaction, water was added and extracted with ethyl acetate (3 $\times$ 6 mL). The combined organic layer was dried (Na_2SO_4), and evaporated under reduced pressure. The title compound was obtained (0.21 g, 90%) after passing through a short silica gel column (hexane/EtOAc 8:2). The data for the compound **10c** was in agreement with the values reported in the literature.^[24]

2-[(1-Hydroxymethylpropylamino)methylene]malonic acid diethyl ester (15a): To the solution of (S)-(+)-2-amino-1-butanol (**15**, 0.500 g, 5.6 mmol) in ethanol (2.5 mL), diethyl ethoxymethylenemalonate (1.13 mL, 5.6 mmol) was added and stirred at room temperature for 30 min. The title compound was obtained as a syrupy liquid (1.42 g, 98%). $[\alpha]_{\text{D}}^{20} = -39.02$ ($c = 1.00$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): $\delta = 0.97$ (t, $J = 7.2$ Hz, 3H), 1.26–1.35 (m, 6H), 1.51–1.71 (m, 2H), 3.20–3.26 (m, 2H), 3.57–3.74 (m, 2H), 4.13–4.25 (m, 4H), 8.05 (d, $J = 14.4$ Hz, 1H), 9.14 ppm (dd, $J_1 = 9.2$, $J_2 = 13.2$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): δ 10.2, 14.2, 14.2, 24.5, 59.5, 59.7, 63.7, 64.7, 89.2, 159.7, 166.3, 169.3 ppm; IR (KBr): $\tilde{\nu} = 465, 547, 674, 751, 805, 1030, 1074, 1148, 1248, 1316, 1379, 1424, 1463, 1608, 1656, 1693, 2876, 2935, 2974, 3276, 3375, 3451$ cm^{-1} ; elemental analysis calcd (%) for $\text{C}_{12}\text{H}_{21}\text{NO}_5$: C 55.58, H 8.16, N 5.40; found: C 51.01, H 8.0, N 5.35.

2-[(1-Ethoxymethylpropylamino)methylene]malonic acid diethyl ester (18): To a dispersion of sodium hydride (0.069 g, 2.8 mmol) in N,N -dimethylformamide (5 mL), **15a** (0.500 g, 1.9 mmol) was added and stirred for 15 min followed by which ethyl bromide (215 μ L, 2.9 mmol) was added under nitrogen atmosphere. After 24 h stirring at room temperature, water was added and extracted with ethyl acetate (3 $\times$ 10 mL). The combined organic layer was dried (Na_2SO_4) and evaporated under reduced pressure. The title compound **18** was obtained as a syrupy liquid (0.38 g, 70%) after purification through column chromatography (hexane/EtOAc 8:2). $[\alpha]_{\text{D}}^{20} = +2.83$ ($c = 1.00$, CHCl_3); ^1H NMR (400 MHz, CDCl_3): $\delta = 0.89$ (t, $J = 7.6$ Hz, 3H), 0.97 (t, $J = 7.6$ Hz, 3H), 1.25–1.36 (m, 6H), 1.50–1.68 (m, 2H), 3.35–3.50 (m, 6H), 4.15–4.27 (m, 4H), 8.06 (d, $J = 14.4$ Hz, 1H), 9.17 ppm (dd, $J_1 = 8.4$, $J_2 = 14.0$ Hz, 1H); ^{13}C NMR (100 MHz, CDCl_3): $\delta = 10.3, 13.8, 14.3, 14.4, 19.2, 25.0, 29.6, 31.5, 59.4, 59.6, 61.6, 71.3, 73.0, 89.2, 159.7, 166.2, 169.3$ ppm; IR (KBr): $\tilde{\nu} = 1606, 1652, 1068, 1151, 1245, 2870$ cm^{-1} ; elemental analysis calcd (%) for $\text{C}_{14}\text{H}_{25}\text{NO}_5$: C 58.52, H 8.77, N 4.87; found: C 58.29, H 8.82, N 4.59.

1-Ethoxymethylpropylamine (18a): Ethylenediamine (465 μ L, 6.9 mmol) was added to a solution of compound **18** (0.500 g, 1.7 mmol) in ethanol (2.5 mL) and the reaction mixture was stirred at room temperature for 1 h. After the completion of the reaction, water (5 mL) was added and extracted with EtOAc (3 $\times$ 4 mL). The combined organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The title compound (0.18 g, 90%) was obtained after passing through a short silica gel column (hexane/EtOAc 3:7). The spectral data for the compound **18a** was in agreement with the literature.^[25]

Acknowledgements

R.G. thanks the UGC-India for the award of the “Research Fellowship in Science for Meritorious Students-2008”. We thank D.S.T-India (F.I.S.T

programme) for the use of 400 MHz NMR spectrometer at the School of Chemistry, Bharathidasan University.

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Received: July 23, 2009

Revised: September 5, 2009

Published online: January 14, 2010