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A CONVENIENT ROUTE TO β-AMINO PROPIONIC ACID DERIVATIVES

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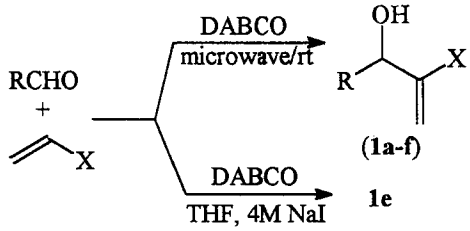
Abstract: A general convenient procedure for the synthesis of β-amino-propionic acid derivatives from Baylis-Hillman adducts is reported.

Peptides containing β-amino acids have recently attracted considerable interest due to their interesting structural and important pharmacological properties[1]. Especially β-alanine has been recognised as a useful building block for inducing β- & γ-turns.[2] In addition β amino acids are important synthons for β-lactam and other bioactive heterocycles. A programme directed towards the utility[3] of the Baylis-Hillman reaction led us to a convenient synthesis of β-aminopropionic acid derivatives.

The Baylis-Hillman (BH) reaction is a carbon-carbon bond formation reaction at the α-position of activated vinylic systems.[3] The Baylis-Hillman adducts with a minimum of three functionality have been exploited for the synthesis of several bioactive molecules or their intermediates.[4] Perlmutter and Tabone[5] have reported preliminary work on the addition of benzylamine to BH adducts,

however, their procedure was restricted only to α-hydroxyalkyl-propionates using benzylamine as nucleophile and using prolonged reaction time. We report herein a convenient general methodology for the synthesis of β-amino propionic acid derivatives starting from acrylates and acrylonitrile using a wide variety of amines.

The Baylis-Hillman coupling of acrylates and acrylonitrile with different aldehydes was acheived either under microwave irradiation[3a] or at ambient condition[3,4] as shown in *Scheme 1*.

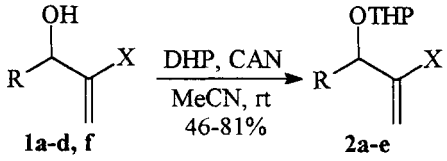


Compound No	R	-X
1a	Ph	CO_2Me
1b	Ph	CO_2Me
1c	4-$(NO_2)C_6H_4$	CO_2Me
1d	Ph	CN
1e	4-$(NO_2)C_6H_4$	CN
1f	2-furyl	CN

Scheme1

In addition, the reaction between p-nitrobenzaldehyde and acrylonitrile was also achieved in the presence of 4M NaI in H_2O medium[6] which gave the adduct **1e** as yellow solid. The BH adducts (**1a-d** and **f**) were converted to tetrahydropyranyl ether in varying yields (46-81%) by treatment with dihydropyran in the presence of

catalytic amount of cerric ammonium nitrate (CAN) in acetonitrile[7] (*Scheme 2, Table 1*).



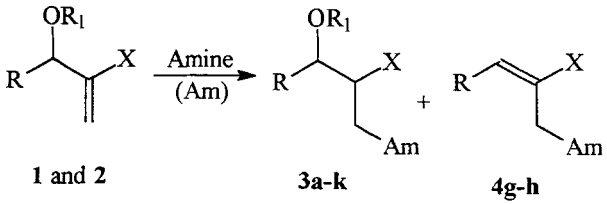
Scheme 2

Table 1: Protection of the hydroxy group of BH adducts

R-	-X	1 : DHP (mmol)	Time (hr.)	2 (%)[a]
CH_3	CO_2Me	1 : 1.5	1.50	**a** (50)
C_6H_5	CO_2Me	1 : 1.5	1.00	**b** (81)
4-$(NO_2)C_6H_4$	CO_2Me	1 : 2.0	0.75	**c** (75)
C_6H_5	CN	1 : 1.5	1.50	**d** (55)
2-furoyl	CN	1 : 1.1	1.00	**e** (46)

a: Yields were based on the products isolated after column chromatography

The BH adducts and their tetrahydropyranyl derivatives were subjected to 1,4-Michael addition with a variety of amines (*Scheme 3*). The conjugate addition of the amines were carried out in different sets, i.e. at 0-10 °C[8] or at room temperature[2b] or at reflux[5] in solvents such as methanol or ethanol. The results are summarized in *Table 2*. All compounds gave satisfactory spectral data.



Scheme 3

Table 2: 1,4-Amine addition to the BH-adducts and derivatives

Entry	R-	R_1-	Amine	-X	Time (hr.) condition	Yield (%)[a]	
						3	**4**
1.	CH_3	H	$NH_2(CH_2)_2OH$	CO_2Me	10/rt.	**a** (94)	—
2.	C_6H_5	H	$NH_2CH_2C_6H_5$	CO_2Me	4.0/rt.	**b** (66)	—
3.	4-$(NO_2)C_6H_4$	H	$NH_2CH(CH_3)_2$	CO_2Me	4.0/rt	**c**(81)	—
4.	C_6H_5	H	piperidine	CO_2Me	12/rt.	**d** (96)	—
5.	C_6H_5	H	$NH_2CH_2C_6H_5$	CN	5.0/rt.	**e** (81)	—
6.	CH_3	THP	$NH_2CH_2C_6H_5$	CO_2Me	4.0/rt.	**f** (35)	—
7.	C_6H_5	THP	$NH_2CH_2C_6H_5$	CO_2Me	4.0/rt.	**g** (59)	**g** (18)
8.	C_6H_5	THP	$NH_2CH(CH_3)_2$	CO_2Me	4.0/rt.	**h** (45)	**h** (25)
9.	4-$(NO_2)C_6H_4$	THP	NH_3	CO_2Me	2.0/rt.	**i** (98)	—
10.	C_6H_5	THP	$NH_2CH_2C_6H_5$	CN	5.0/rt.	**j** (97)	—
11.	2-furyl	THP	$NH_2CH_2C{\equiv}CH$	CN	1.5/rt.	**k** (34)	—

a: Yields were based on the products isolated

The tetrahydropyranyl derivatives of Baylis-Hillman adducts **2** underwent usual Michael addition to afford β-aminoesters **3a-k** in moderate yields. The formation of the addition-elimination products **4g-h** was also observed when BH adduct was reacted with benzylamine and isopropylamine respectively (entry 7 and 8, *Table 2*).

Studies on the utility of the amino adducts and their biological activities will be the subject of our further communications.[9]

Experimental[11]

Synthesis of 2-methylene-3-hydroxy-3-(4'-nitrophenyl))propionitrile (1e): To a mixture of p-nitrobenzaldehyde (3.0 gm, 20 mmol) acrylonitrile (1.1 gm, 20.7 mmol) and DABCO (0.12 gm, 1.0 mmol) in tetrahydrofuran (5 ml) was added aqueous NaI (4M, 2 ml) dropwise at room temperature and stirring was continued for 2 h. The usual workup followed by extraction with ether, washing of the

organic layer with brine and drying over sodium sulphate, removal of ether under vacuo and purification by column chromatography over silica gel gave **1e** (1.53 gm, 37.8%), m. p. 71-73 °C IR (Kbr) cm^{-1}: 3440 (OH), 2260 (C≡N), ^1H NMR ($CDCl_3$+ D_2O) δ 8.25 (d, 2H, J=~8 Hz), 7.70 (d, 2H, J=~8 Hz), 6.15 (d, 2H, J=~6 Hz) 5.48 (bs, 1H), 3.08 (s, 1H).

Typical procedure for the synthesis of THP derivatives of the Baylis-Hillman adducts (2a-e): To a stirred mixture of dihydropyran (1.0-2.0 mmol) and catalytic amount of cerric ammonium nitrate (20 mg-60 mg) in acetonitrile (5-10 ml) was added the respective Baylis-Hillman adduct (1 mmol) dropwise and after complete addition the resultant reaction mixture was stirred for the period mentioned in the *Table 1*. The reaction mixture was extracted with ether, washed with brine, dried over sodium sulphate and subjected to column chromatography to afford the compounds **2a-e**. *Compound 2a:* IR (neat) cm^{-1}: 1740 (C=O). ^1H NMR ($CDCl_3$) δ: 6.27 (s, 1H, olefinic H), 5.85 (s, 1H, olefinic H), 5.00 (s, 1H, allylic H), 4.80 & 4.20 (bt, 1H, diastereomeric -O-C<u>H</u>-O-), 3.80 (s, 3H, O<u>CH</u>$_3$), 3.60 (bt, 2H, O<u>CH</u>$_2$-), 1.70 (s, 6H, ring -<u>CH</u>$_2$-). Spectral details of other derivatives were in agreement with their structures.

Synthesis of methyl(3-hydroxy-(2-(2-hydroxy)aminomethyl))butyrate 3a: To a stirred mixture of ethanolamine (244 mg, 4 mmol), triethylamine (404 mg, 4 mmol), in ethanol (5 ml) methyl(3-hydroxy-2-methylene)butyrate (**1a**) (520 mg, 4 mmol) in ethanol (5 ml) was added dropwise and after complete addition the resultant mixture was stirred for a total period of 10 hr. at room temperature. After completion of reaction ethanol was removed in vacuo, the residue was purified by column chromatography to give **3a** (720 mg, 94%). IR (neat) cm^{-1}: 3380 (OH), 1730 (C=O). ^1H NMR ($CDCl_3$ + D_2O) δ: 3.70 (bs, 5H, -O<u>CH</u>$_3$ and -O<u>CH</u>$_2$), 2.80-2.25 (m, 9H, CH_3<u>CH</u>(OH)-), -N<u>CH</u>$_2$, -<u>CH</u>CO_2Me, -N<u>H</u> and -O<u>H</u>), 1.20 (d, 3H, J=6 Hz, -<u>CH</u>$_3$).

Typical procedure for the synthesis of β-amino acid derivatives (3b-k): To a solution of the respective Baylis-Hillman adducts **1** or **2** (1 mmol) in methanol (3 ml), was added the respective amines (1.1 mmol) in methanol (3 ml) dropwise at room temperature under stirring and after complete addition the resultant reaction mixture was allowed to stir for the period mentioned in *Table 2*. The usual workup followed by removal of methanol in vacuo, purification of the residue by column chromatography over silica gel using petroleum ether/ethyl acetate as eluent gave β-amino esters and nitriles (**3b-k**).

*Methyl((3-hydroxy-3-(4-nitrophenyl)-2-isopropylaminomethyl)propionate **3c***: IR (neat) cm^{-1}: 3460 (b, OH), 1720 (C=O). ^1H NMR ($CDCl_3$ + D_2O) δ: 8.20 (d, 2H, J=~8 Hz, aromatic H), 7.60 (d, 2H, J=~8 Hz, aromatic H), 5.40 (m, 1H, -C<u>H</u>(OH)-), 4.00 (bs, 2H, -O<u>H</u>, -N<u>H</u>), 3.70 (s, 3H, -OC<u>H</u>$_3$), 3.20-2.60 (m, 4H, -C<u>H</u>(CO_2Me)-, -C<u>H</u>$_2$NH-, -NHC<u>H</u>(Me)$_2$), 1.10 (d, 3H, J=~8 Hz, -C<u>H</u>$_3$).

*Methyl(3-hydroxy-3-phenyl-(2-piperidinomethyl))propionate **(3d)***: IR (neat) cm^{-1}: 3387 (OH), 1736 (C=O). ^1H NMR ($CDCl_3$ + D_2O) δ: 7.30 (s, 5H, aromatic H), 5.25 & 4.90 (d & m, 1H, J=~6 Hz, diastereomeric -C<u>H</u>(OH)-), 4.75 (bs, 1H, -O<u>H</u>), 3.65 & 3.40 (s, 3H, diastereomeric -OC<u>H</u>$_3$), 2.80-2.20 (bm, 5H, -C<u>H</u>(CO_2Me)-, -C<u>H</u>$_2$NH-, -NHC<u>H</u>$_2$-), 1.50 (bs, 6H, ring -C<u>H</u>$_2$).

*(3-hydroxy-3-phenyl-(2-benzylaminomethyl))propionitrile **3e***:IR (neat) cm^{-1}: 3440 (OH), 2260 (CN). ^1H NMR ($CDCl_3$ + D_2O) δ: 7.30 (s, 10H, aromatic H), 4.90 (bd, 1H, Ph C<u>H</u>(OH)-), 3.80 (m, 2H, -NHC<u>H</u>$_2$Ph), 3.10 (m, 2H, -C<u>H</u>$_2$NH-), 2.60 (bm, 3H, -C<u>H</u>(CO_2Me)-, -O<u>H</u> and -N<u>H</u> protons).

*Methyl(3-(tetrahydropyran-2-yl)oxy-(2-benzylaminomethyl))butyrate **3f**:* IR (neat) cm^{-1}: 3347 (OH), 1740 (C=O). ^1H NMR ($CDCl_3$) δ: 7.30 (s, 5H, aromatic H), 4.63 (s, 1H, -OC<u>H</u>O-), 4.03 (m, 1H, -OC<u>H</u>$_2$-), 3.86 (m, 1H, -OC<u>H</u>$_2$-), 3.78 (m, 2H, -NHC<u>H</u>$_2$-), 3.69 (s, 3H, -OC<u>H</u>$_3$), 3.47 (m, 1H, -C<u>H</u>(OTHP)-), 2.98 (dd, 1H,

J=~11 Hz, -CH(OTHP)-), 2.84 (d, 1H, J=~11 Hz), 2.76 (m, 1H, -CH(CO_2Me)-), 1.48 (bs, 6H, ring -CH_2), 1.25 (d, 3H, J=6.3 Hz, -CH_3). EIMS: 322 (M^++1).

Methyl(3-(tetrahydropyran-2-yl)oxy-3-phenyl-(2-benzylaminomethyl))propionate ***3g:*** IR (FT, neat) cm^{-1}: 1740 (C=O). ^1H NMR ($CDCl_3$) δ: 7.29 (s, 10H, aromatic H), 4.96 & 4.88 (2d, 1H, J=8.5 Hz & 7.8 Hz, diastereomeric -CH(OTHP)-), 4.78 & 4.38 (2 bs, 1H, diastereomeric -OCHO-), 3.79 (s, 2H, -NHCH_2-), 3.50 (s, 2H, -OCH_2-), 3.46 (s, 3H, -OCH_3), 3.13 (d, 2H, J=6 Hz, -CH_2NH-), 3.04 (m, 1H, -CH(CO_2Me)-), 1.55 (bs, 6H, ring -CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 173.28, 140.44, 139.62, 128.79, 128.39, 128.31, 127.70, 127.11, 126.97, 99.85, 94.99, 78.40, 62.34, 54.02, 51.71, 48.65, 47.60, 30.59, 25.57, 19.29. EIMS (m/z): 385 (M^+).

Methyl(3-tetrahydropyran-2-yl)oxy-3-phenyl-(2-isopropylamiomethyl)propionate ***(3h):*** IR (FT, neat) cm^{-1}: 1740 (C=O). ^1H NMR ($CDCl_3$) δ: 7.40 (s, 5H, aromatic H), 5.06 (bm,1H, -CH(OTHP)-), 4.56 (m, 1H, -OCHO-), 3.93 (m, 2H, -OCH_2-), 3.63 (s, 3H, -OCH_3), 3.33-3.03 (bm, 3H, -CH(CO_2Me)-, -CH_2NH-), 2.90-2.73 (bm, 1H, -NHCH-), 1.64 (bs, 7H, ring -CH_2 and -NH), 1.56 (d, 3H, J=6 Hz, -CH_3). EIMS (m/z): 336 (M^+ +1), 337 (M^++2).

Methyl(((3-(tetrahydropyran-2yl)oxy-3-(4-nitrophenyl))-2-aminomethyl)) propionate ***(3i)***: IR ($CHCl_3$) cm^{-1}: 1740 (C=O). ^1H NMR ($CDCl_3$ + D_2O) δ: 8.15 (d, 2H, J=~8 Hz, aromatic H), 7.55 (d, 2H, J=~8 Hz, aromatic H), 4.80 (bd, 1H, -CH(OTHP)-), 4.30 (bs, 1H, -OCHO-), 3.80 (bs, 2H, -OCH_2-), 3.50 (s, 3H, -OCH_3), 3.30-2.70 (bm, 3H, -CH(CO_2Me)-, -CH_2NH-), 1.90 (bs, 2H, -NH_2), 1.60 (bs, 6H, ring -CH_2).

(3-(Tetrahydropyran-2-yl)oxy-3-phenyl-(2-benzylaminomethyl)))propionitrile(3j): IR (neat) cm^{-1}: 2240 (CN). ^1H NMR ($CDCl_3$) δ: 7.76 (s, 10H, aromatic H), 5.20 (bd, 1H, -CH(OTHP)-), 4.20-3.70 (m, 5H, -NHCH_2-, -OCHO-, -OCH_2-), 3.26-2.83 (m, 3H, -CH(CO_2Me)-, -CH_2NH-), 1.70 (bs, 6H, ring -CH_2-).

(3-(Tetrahydropyran-2-yl)oxy-3-furoyl-(2-(prop-2-yne)aminomethyl))propionitrile (3k): IR (FT, neat), cm^{-1}: 2248 (CN), 2212 (C≡C). ^1H NMR ($CDCl_3$ + D_2O) δ: 7.30 (s, 1H, aromatic H), 6.30 (m, 2H, aromatic H), 4.90 (d, 1H, J=~6 Hz, -CH(OTHP)-), 4.46 (bt, 1H, -OCHO-), 3.70-2.70 (m, 7H, -CH(CO_2Me)-, -CH_2(NH_2)-, -NHCH_2-, ring -OCH_2-), 2.16 (bs, 1H, acetylenic H), 1.63 (bs, 6H, ring -CH_2).

Methyl(3-phenyl-2-isopropylaminomethyl)pro-2-enoate (4g): IR (Neat) cm^{-1} :1725 (ester C=O). ^1H NMR ($CDCl_3$) δ: 7.92 (s, 1H, olefinic H), 7.49 (m, 2H, aromatic H & olefinic H), 7.36 (m, 4H, aromatic H), 3.81 & 3.76 (s, 3H, E & Z -OCH_3), 3.58 (s, 2H, -CH_2NH-), 2.81 (m, 1H, -NHCH-), 0.98 & 0.91 (d, 6H, J=6.6 Hz, -CH_3). EIMS (m/z): 233 (M^+). Spectral data of the compound **4h** were also in agreement with the structure.

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11. Silica gel (100-200 mesh) was used for column chromatography with petroleum ether/ethyl acetate as eluant. IR spectra were recorded with a Perkin-Elmer 681 spectrometer. NMR spectra were recorded at 60 MHz (CW, EM 360, Varian and FT, Hitachi-R-600), 500 MHz (Bruker, AM-500) in $CDCl_3$ using TMS as internal standard, J values are given in Hz. Mass spectra were recorded with Shimadzu MS-QP 1000 spectrometer at 70 ev.

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