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DBU-mediated C-C bond formation between Baylis-Hillman acetates and active methylene compounds

Sonam Tashi Khom, Pranjit Saikia & Nagendra Nath Yadav*

Department of Chemistry, North Eastern Regional Institute of Science and Technology, Nirjuli, Arunachal Pradesh 791 109, India

E-mail: nny@nerist.ac.in

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A new reagent system for the formation of C-C bond between the Baylis-Hillman acetates and active methylene compounds (AMCs) has been developed. This method provides tri-substituted alkenes as the major product in good yield under neat condition. The reaction proceeds through the S_N2' mechanism to give substituted alkenes in good yields with high stereoselectivity. 1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) acts as a unique base which accelerates the rate of the reaction.

Keywords: Baylis-Hillman acetates, S_N2' Substitution, DBU, Active methylene compounds, Tri-substituted alkenes

The carbon-carbon bond-forming reactions are very important in organic synthesis. The Morita-Baylis-Hillman reaction has become one of the most useful and popular synthetic routes for the formation of new C-C bonds[1] with immense synthetic utility, promise, and potential. The easy availability and multi-functional nature of Morita-Baylis-Hillman adducts makes them an important scaffold for the synthesis of a variety of heterocycles such as β-lactones, pyran-2-ones, aziridines, azetidines, β-lactams, quinolones, indolizines, piperidines, pyrrolidines and isoxazolines as well as natural products and biologically active compounds including tacamonine, nuciferol, asmarines A and B, mikanecic acids, diversonol and phaseolinic acids[1-10]. Baylis-Hillman acetates derived from corresponding adducts prove to be potential electrophiles that can react with a variety of nucleophiles. Their capacity to undergo S_N2' allylic substitution reactions is a major factor in their synthetic utility[11-21]. As a result, a variety of nucleophiles, such as azides, indoles, phenylacetylene, halides, and active methylene compounds have been used to construct a wide range of synthetic intermediates[22-29]. Kim *et al.* reported the allylic rearrangement products from Baylis-Hillman acetates and active methylene compounds in presence of K_2CO_3 in acetonitrile at room temperature in 24 hrs[30]. Kim *et al.* also reported DABCO catalyzed normal substitution products from Baylis-Hillman acetates and acetylacetone followed by K_2CO_3 catalyzed Michael type 6-endo-trig cyclization to afford highly functionalized 3,4-dihydro-2*H*-pyrans in 30-63% yields[31]. W. Su *et al.* reported Et_3N mediated allylic substitution of Baylis-Hillman acetates with cyclohexane-1,3-diones followed by cyclization to get 3-arylmethyl-7,8-hydro-6*H*-chromene-2,5-diones and 2-Hydroxy-7,8-dihydroquinolin-5(6*H*)-ones at 90°C[32,33]. The efficiency of DBU as a non-nucleophilic, sterically hindered, tertiary amine base in organic chemistry has been well documented in the literature[34,35]. Because of the numerous applicability of substituted alkenes in making synthetic drugs and naturally occurring biologically active compounds, there is scope to develop new and efficient protocols for these tri-substituted alkenes. So, herein we report facile and efficient synthesis of tri-substituted olefins from Baylis-Hillman acetates and active methylene compounds using DBU as a mild reagent under neat condition.

Experimental Section

All chemicals and materials were of reagent grade as received from commercial outlets. The solvents were used without further purification. Baylis-Hillman acetates were prepared as reported[1-4,36-40]. Reaction progress was monitored using TLC silica gel 60 F_{254} manufactured by Merck KGaA. Purification of the products was carried out by column chromatography using 60-120 mesh silica gel manufactured by Merck life science private limited. IR spectra were determined on Nicolets iS5, Thermo Fischer Scientific. The ^1H and ^{13}C NMR were

recorded on a Bruker Avance 400 MHz/Avlll HD-300 MHz spectrometer with TMS as the internal standard and $CDCl_3$ as solvent. High-resolution mass spectrometry (HRMS) was determined on Agilent 6520 (Q-TOF) Mass spectrometer with Agilent 1200 HPLC system.

General Procedures

1 mmol of Baylis-Hillman acetates (**1**, 1.0 equiv.) was taken in a round bottom flask (10 cm^3), were added active methylene compounds (**2**, 1.2 equiv.) On stirring, DBU (1.5 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 1-4 hrs. After the complete conversion of starting material as confirmed by TLC, the reaction mixture was quenched with 2N HCl (3ml) and extracted with CH_2Cl_2 (3 × 20 ml). The combined organic layers were then washed with $NaHCO_3$ (2 × 20 ml) and with brine and dried over anhydrous Na_2SO_4. Filtration and solvent removal under vacuum provided the crude as a viscous liquid which was purified by column chromatography using ethyl acetate/ hexane as eluent to get the pure product **3**. The spectroscopic and analytical data of representative tri-substituted olefins are given below.

(*E*)-Triethyl 4-phenylbut-3-ene-1,1,3-tricarboxylate, 3a: Viscous oil, IR (KBr): 2984, 1736, 1451, 1385 1250, 1093, 826, 763, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.41–7.29 (m, 5H), 4.28 (q, J = 7.1 Hz, 2H), 4.11–4.02 (m, 4H), 3.81 (t, J = 7.9 Hz, 1H), 3.22 (d, J = 7.9 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H), 1.15 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4, 167.0, 141.2, 138.3, 134.6, 129.0, 128.4, 128.1, 61.2, 60.8, 50.3, 26.1, 14.1, 13.8; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{19}H_{25}O_6$: 349.1651; found: 349.1659.

(*E*)-Diethyl 2-benzylidene-4-cyanopentanedioate, 3b: Viscous oil, IR (KBr): 2917, 2365, 1745, 1384, 1216, 1024, 804, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.47–7.33 (m, 5H), 4.29 (q, J = 7.1 Hz, 2H), 4.22–4.13 (m, 2H), 4.08 (t, J = 8.1 Hz, 1H), 3.16 (d, J = 8.8 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 165.7, 144.1, 134.5, 129.2, 129.1, 128.8, 127.0, 116.2, 63.0, 61.5, 36.4, 27.7, 14.3, 13.9; HRMS (ESI): m/z: $[M + H]^+$ calcd. for $C_{17}H_{20}NO_4$: 302.1392; found: 302.1393.

(*E*)-Diethyl 2-acetyl-4-benzylidenepentanedioate, 3c: Viscous oil, IR (KBr): 2978, 2356, 1718, 1449, 1385, 1253, 1093, 854, 774, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.46–7.23 (m, 5H), 4.28 (q, J = 7.1 Hz, 2H), 4.14–3.94 (m, 2H), 3.84 (dd, J = 7.9, 6.9 Hz, 1H), 3.22 (dd, J = 14.4, 8.2 Hz, 1H), 3.07 (dd, J = 14.3, 6.6 Hz, 1H), 2.14 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.14 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.4, 169.5, 167.7, 141.6, 135.2, 129.5, 129.2, 128.8, 128.7, 61.5, 61.2, 58.4, 28.9, 25.6, 14.4, 14.0; HRMS (ESI): m/z: $[M + H]^+$ calcd. for $C_{18}H_{23}O_5$: 319.1545; found: 319.1541.

(*Z*)-Diethyl 2-(2-cyano-3-phenylallyl)malonate, 3d: Viscous oil, IR (KBr): 2968, 2345, 1707, 1423, 1259, 887, 716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75–7.67 (m, 2H), 7.45–7.36 (m, 4H), 4.28–4.17 (m, 4H), 3.78 (t, J = 7.7 Hz, 1H), 3.00 (d, J = 7.7 Hz, 2H), 1.26 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.1, 146.4, 133.3, 130.5, 129.0, 128.9, 118.0, 106.9, 62.1, 50.7, 35.3, 14.1; HRMS (ESI): m/z: $[M + H]^+$ calcd. for $C_{17}H_{20}NO_4$: 302.1392; found: 302.1403.

(*E*)-Triethyl 4-(4-chlorophenyl)but-3-ene-1,1,3-tricarboxylate, 3e: Viscous oil, IR (KBr): 2984, 2357, 1725, 1490, 1372, 1238, 1087, 1014, 861, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.40–7.31 (m, 4H), 4.29 (q, J = 7.1 Hz, 2H), 4.18–4.02 (m, 4H), 3.81 (t, J = 7.9 Hz, 1H), 3.17 (d, J = 7.9 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 167.3, 140.3, 134.6, 133.5, 130.6, 129.7, 128.9, 61.5, 61.2, 50.4, 26.3, 14.3, 14.0; HRMS (ESI): m/z $[M + H]^+$ calcd. for $C_{19}H_{24}ClO_6$: 383.1261; found: 383.1265.

(*E*)-Diethyl 2-acetyl-4-(4-chlorobenzylidene) pentanedioate, 3f: Viscous oil, IR (KBr): 2986, 1718, 1494, 1374, 1244, 1086, 1011, 841, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.40–7.30 (m, 4H), 4.28 (q, J = 7.1 Hz, 2H), 4.16–3.97 (m, 2H), 3.85 (dd, J = 8.1, 6.7 Hz, 1H), 3.16 (dd, J = 14.7, 7.9 Hz, 1H), 3.08–2.99 (m, 1H), 2.17 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.3, 169.5, 167.6, 140.4, 134.9, 133.7, 130.7, 130.2, 129.1, 61.7, 61.2, 58.3, 29.2, 25.7, 14.5, 14.0; HRMS (ESI): m/z: $[M + H]^+$ calcd. for $C_{18}H_{22}ClO_5$: 353.1156; found: 353.1150.

(*E*)-Triethyl 4-(4-methoxyphenyl)but-3-ene-1,1,3-tricarboxylate, 3g: Viscous oil, IR (KBr): 2987, 2366, 1732, 1608, 1515, 1464, 1373, 1250, 1091 834, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.41 (d, J = 8.5 Hz, 2H), 6.92 (d, J = 8.6 Hz, 2H), 4.27 (q, J = 7.1 Hz, 2H), 4.17–4.03 (m, 4H), 3.86–3.78 (m, 4H), 3.24 (d, J = 7.9 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.1 Hz, 6H); ^{13}C NMR

(75 MHz, $CDCl_3$) δ 169.0, 167.8, 160.0, 141.2, 131.1, 127.4, 126.7, 114.0, 61.3, 60.9, 55.2, 50.5, 26.3, 14.2, 13.9; HRMS (ESI): m/z: $[M + H]^+$ calcd. for $C_{20}H_{27}O_7$: 379.1757; found: 379.1742.

(*E*)-Diethyl 2-acetyl-4-(4-methoxybenzylidene) pentanedioate, 3h: Viscous oil, IR (KBr): 2978, 2357, 1717, 1611, 1515, 1467, 1263, 1091, 836, 757 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.71 (s, 1H), 7.39 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 4.19–3.99 (m, 2H), 3.88–3.78 (m, 4H), 3.25 (dd, J = 14.4, 8.2 Hz, 1H), 3.10 (dd, J = 14.4, 6.7 Hz, 1H), 2.18 (s, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 169.5, 167.9, 160.0, 141.1, 131.1, 127.4, 127.1, 114.1, 61.4, 60.9, 58.2, 55.3, 28.9, 25.6, 14.3, 13.9; HRMS (ESI): m/z: $[M + Na]^+$ calcd. for $C_{19}H_{24}NaO_6$: 371.1471; found: 371.1457.

(*E*)-Diethyl 2-cyano-4-(4-methoxybenzylidene) pentanedioate 3i: Viscous oil, IR (KBr): 2981, 2360, 1731, 1599, 1457, 1382, 1260, 1090, 830, 761 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.90 (s, 1H), 7.40 (d, J = 8.6 Hz, 2H), 6.95 (d, J = 8.8 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 4.26–4.15 (m, 2H), 4.10 (dd, J = 9.0, 7.4 Hz, 1H), 3.84 (s, 3H), 3.30–3.13 (m, 2H), 1.37 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.3, 165.9, 160.4, 143.7, 131.1, 126.9, 124.7, 116.3, 114.4, 63.0, 61.4, 55.4, 36.4, 27.8, 14.3, 14.0; HRMS (ESI): m/z: $[M + H]^+$ calcd. for $C_{18}H_{22}NO_5$: 332.1498; found: 332.1488.

(*E*)-Triethyl 4-(4-nitrophenyl)but-3-ene-1,1,3-tricarboxylate, 3j: Viscous oil, IR (KBr): 2985, 1731, 1598, 1522, 1350, 1025, 858, 702 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.26 (d, J = 8.5 Hz, 2H), 7.78 (s, 1H), 7.56 (d, J = 8.5 Hz, 2H), 4.32 (q, J = 7.0 Hz, 2H), 4.19–4.04 (m, 4H), 3.84 (t, J = 7.8 Hz, 1H), 3.13 (d, J = 7.8 Hz, 2H), 1.37 (t, J = 7.0 Hz, 3H), 1.20 (t, J = 7.1 Hz, 6H). ^{13}C NMR (101 MHz, CDCl3) δ 168.7, 166.7, 147.5, 141.7, 139.1, 132.3, 129.9, 123.8, 61.7, 50.2, 29.8, 26.5, 14.3, 14.0; HRMS (ESI): m/z: $[M + Na]^+$ calcd. for $C_{19}H_{23}NNaO_8$: 416.1321; found: 416.0967.

(*E*)-Diethyl 2-cyano-4-(4-nitrobenzylidene) pentanedioate, 3k: Viscous oil, IR (KBr): 2977, 2347, 1731, 1511, 1203, 1021, 848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8.7 Hz, 2H), 7.99 (s, 1H), 7.56 (d, J = 8.4 Hz, 2H), 4.34 (q, J = 7.1 Hz, 2H), 4.27–4.10 (m, 4H), 3.20–3.00 (m, 1H), 1.39 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.2, 165.4, 147.9, 141.6, 141.2, 130.2, 129.9, 124.1, 116.1, 63.3, 62.0, 29.8, 27.8, 14.3, 14.1; HRMS (ESI): m/z: $[M + H]^+$ calcd. for $C_{17}H_{19}N_2O_6$: 347.1243; found: 347.1241.

(*E*)-Ethyl 4-acetyl-2-benzylidene-5-oxohexanoate, 3l: Viscous oil, IR (KBr): 2962, 2366, 1707, 1453, 1385, 1267, 1092, 866, 769, 704 cm^{-1}; ^1H NMR (300 MHz, CDCl3) δ 7.78 (s, 1H), 7.44–7.33 (m, 5H), 4.28 (q, J = 7.1 Hz, 2H), 3.95 (t, J = 6.9 Hz, 1H), 3.11 (d, J = 6.9 Hz, 2H), 2.04 (s, 6H), 1.35 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.8, 167.5, 141.5, 134.8, 129.5, 128.9, 128.6, 128.6, 67.1, 61.1, 28.9, 25.4, 14.1; HRMS (ESI): m/z: $[M + H]^+$ calcd. for $C_{17}H_{21}O_4$: 289.1440; found: 289.1436.

(*E*)-Ethyl 4-acetyl-2-(4-chlorobenzylidene)-5-oxohexanoate, 3m: Viscous oil, IR (KBr): 2988, 1699, 1489, 1382, 1261, 1094, 1015, 830, 716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.44–7.26 (m, 4H), 4.28 (q, J = 7.1 Hz, 2H), 3.99 (t, J = 6.9 Hz, 1H), 3.06 (d, J = 6.9 Hz, 2H), 2.08 (s, 6H), 1.35 (t, J = 7.1 Hz, 3H). 13C NMR (75 MHz, $CDCl_3$) δ 203.6, 167.4, 140.3, 133.5, 131.6, 130.5, 130.2, 129.0, 67.0, 61.4, 29.3, 25.6, 14.3; HRMS (ESI): m/z: $[M + H]^+$ calcd. for $C_{17}H_{20}ClO_4$: 323.1050; found: 323.1068.

(*E*)-Ethyl 4-acetyl-2-(4-methoxybenzylidene)-5-oxohexanoate, 3n: Viscous oil, IR (KBr): 2981, 2358, 1697, 1605, 1508, 1260, 1095, 1025, 835, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.34 (d, J = 8.6 Hz, 2H), 6.92 (d, J = 8.7 Hz, 2H), 4.26 (q, J = 7.1 Hz, 2H), 4.00 (t, J = 6.9 Hz, 1H), 3.83 (s, 3H), 3.14 (d, J = 6.9 Hz, 2H), 2.09 (s, 6H), 1.34 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 204.0, 167.9, 160.1, 141.2, 131.0, 127.3, 127.2, 114.1, 67.0, 61.1, 55.3, 29.2, 25.6, 14.2; HRMS (ESI): m/z: $[M + Na]^+$ calcd. for $C_{18}H_{22}NaO_5$: 341.1365; found: 341.1340.

(*Z*)-4-Benzoyl-2-(4-nitrobenzylidene)-5-oxo-5-phenylpentanenitrile, 3o: Viscous oil, IR (KBr): 2930, 2212, 1684, 1515, 1249, 1030, 823, 687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 8.7 Hz, 1H), 8.16 (d, J = 8.7 Hz, 1H), 7.94 (d, J = 7.9 Hz, 3H), 7.69 (d, J = 8.6 Hz, 1H), 7.57–7.49 (m, 3H), 7.46–7.37 (m, 5H), 7.19 (s, 1H), 5.68 (t, J = 7.0 Hz, 1H), 3.17 (d, J = 7.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.3, 144.4, 135.4, 134.3, 129.5, 129.3, 129.3, 128.7, 124.1, 117.8, 111.9, 54.0, 35.7; HRMS (ESI): m/z: $[M + H]^+$ calcd. for $C_{25}H_{19}N_2O_4$: 411.1345; found: 411.1346.

(*Z*)-4-Benzoyl-2-(4-nitrobenzylidene)-5-oxohexanenitrile, 3p: Viscous oil, IR (KBr): 2935, 2347, 1709, 1452, 1089, 802 cm^{-1}; ^1H NMR

(500 MHz, $CDCl_3$) δ 8.23 (d, J = 8.8 Hz, 2H), 8.05 (d, J = 7.3 Hz, 2H), 7.78 (d, J = 8.8 Hz, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.55 (t, J = 7.7 Hz, 2H), 7.16 (s, 1H), 5.00 (t, J = 7.1 Hz, 1H), 3.18–3.04 (m, 2H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 201.0, 194.8, 144.0, 137.1, 135.9, 134.6, 130.0, 129.6, 129.4, 129.0, 124.2, 117.5, 111.9, 59.7, 35.0, 29.5; HRMS (ESI): m/z: $[M + H]^+$ calcd. for $C_{20}H_{17}N_2O_4$: 349.1188; found: 349.1187.

(*E*)-Ethyl-4-benzoyl-2-(4-nitrobenzylidene)-5-oxo-5-phenylpentanoate, 3q: Viscous oil, IR (KBr): 2930, 2352, 1706, 1519, 1347, 1254, 848, 687 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.20 (d, J = 8.7 Hz, 2H), 8.03 (d, J = 7.4 Hz, 1H), 7.93 (d, J = 7.4 Hz, 3H), 7.70 (s, 1H), 7.57–7.49 (m, 4H), 7.40 (t, J = 7.8 Hz, 4H), 5.84 (t, J = 7.1 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.30 (d, J = 7.1 Hz, 2H), 1.34 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 167.3, 147.5, 141.9, 139.6, 135.9, 133.8, 132.4, 129.9, 129.0, 128.8, 123.8, 61.6, 55.2, 27.7, 14.3; HRMS (ESI): m/z: $[M + H]^+$ calcd. for $C_{27}H_{24}NO_6$: 458.1604; found: 458.1605.

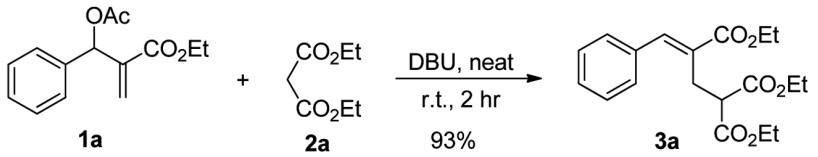
(*E*)-Ethyl-4-benzoyl-2-(3-nitrobenzylidene)-5-oxo-5-phenylpentanoate, 3r: Viscous oil, IR (KBr): 2936, 2344, 1709, 1523, 1342, 760, 704 cm^{-1}; 1H NMR (500 MHz, $CDCl_3$) δ 8.15 (d, J = 8.2 Hz, 1H), 8.06–8.00 (m, 2H), 7.93 (d, J = 7.4 Hz, 3H), 7.79 (d, J = 7.7 Hz, 1H), 7.70 (s, 1H), 7.60–7.50 (m, 3H), 7.40 (t, J = 7.8 Hz, 4H), 5.83 (t, J = 7.2 Hz, 1H), 4.29 (q, J = 7.1 Hz, 2H), 3.31 (d, J = 7.1 Hz, 2H), 1.34 (t, J = 7.2 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.7, 167.3, 148.2, 139.5, 136.9, 135.9, 134.7, 133.7, 132.0, 129.6, 128.9, 128.7, 124.1, 123.2, 61.5, 55.2, 27.6, 14.3; HRMS (ESI): m/z: $[M + H]^+$ calcd. for $C_{27}H_{24}NO_6$: 458.1604; found: 458.1606.

Results and Discussion

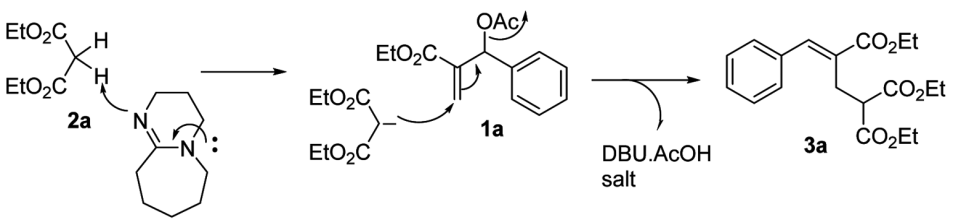
In continuation of our research on the Baylis-Hillman chemistry[29,41], we developed a new method for the regio- and stereo selective synthesis of tri-substituted olefins in good yields (56–93%). Accordingly, we treated Baylis-Hillman acetate *i.e.* 3-acetoxy-2-methylene-3-phenylpropanoate (**1a**) derived from benzaldehyde and ethyl acrylate with diethyl malonate (**2a**) as active methylene compound in presence of 1,8-diazabicyclo(5.4.0) undec-7-ene (DBU) as a unique base without using solventat room temperature for 2 hrs to give (E)-triethyl 4-phenylbut-3-ene-1,1,3-tricarboxylate (**3a**) in 93% yield (Scheme 1).

The mechanism for the formation of trisubstituted alkene **3a** is described in Scheme 2. First DBU will abstract the acidic proton from active methylene compound **2a** to give resonance stabilized carbanion which preferably reacts at γ-position of Baylis-Hillman acetate to give γ-substituted product **3a** (Scheme 2). The Baylis-Hillman acetates undergo Michael type addition reaction followed by acetoxy elimination with carbon nucleophiles. The role of DBU in this reaction is to accelerate the reaction by neutralizing the free acetic acid formed in the reaction as a side product.

The formation of desired product from Baylis-Hillman acetate and diethyl malonate under mild reaction condition using DBU as unique base in short reaction time encouraged us to screen various inorganic and organic bases under different reaction conditions (Table 1). Use of K_2CO_3 under neat condition gives only 72% yield of product after 20 hrs, while use of acetonitrile as solvent along with K_2CO_3 gave the desired product in 81% yield[30]. Cesium carbonate under neat condition gave poor yields (Table 1, entry 1-3). Organic bases such as pyridine,



Scheme 1 — Synthesis of (*E*)-triethyl 4-phenylbut-3-ene-1,1,3-tricarboxylate (**3a**).



Scheme 2 — Plausible reaction mechanism for formation of tri-substituted alkene **3a**

Table 1 — Screening of different bases for the synthesis of tri-substituted alkenes **3a**

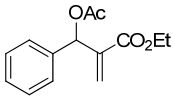
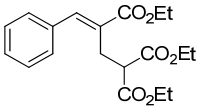
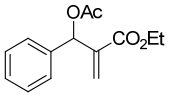
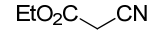
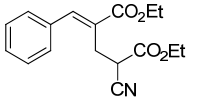
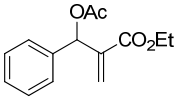
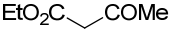
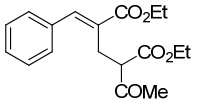
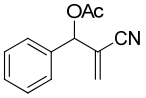
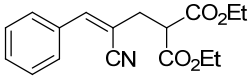
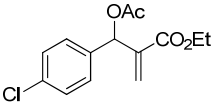
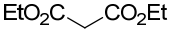
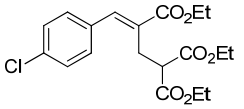
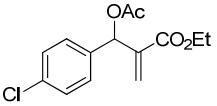
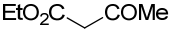
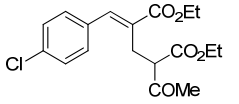
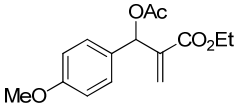
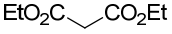
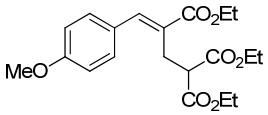
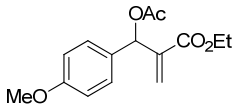
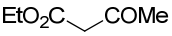
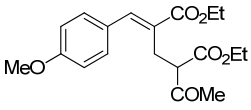
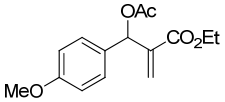
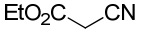
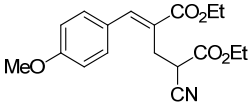
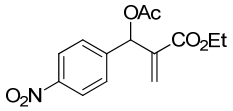
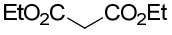
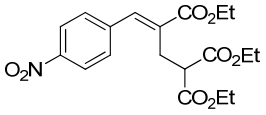
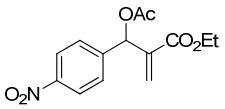
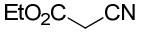
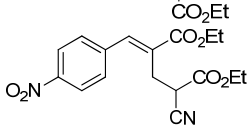
Entry	Base (1.2 eq)	Time (h)	Solvent	Yield (%)[a]
1	K_2CO_3	20	neat	72
2	K_2CO_3	24	CH_3CN	81[b]
3	Cs_2CO_3	25	neat	48
4	Pyridine	16	neat	55
5	DIPEA	12	neat	40
6	Et_3N	8	neat	54
7	**DBU**	**2**	**neat**	**93**
8	DBU	12	CH_2Cl_2	71

[a]Isolated yield; [b]ref 30.

diisopropylethylamine (DIPEA) and triethylamine under neat condition provided low yields. DBU under neat condition was found to be more effective for this reaction based on high yield and shorter reaction time (Table 1, entry 7).

Once we optimized the reaction condition for synthesis of tri-substituted olefins from Baylis-Hillman acetate, next we attempted the reaction of several other substituted Baylis-Hillman acetates and various ester containing active methylene compounds under the same reaction condition (Table 2 and 3).

Table 2 — Synthesis of diversified tri-substituted alkenes using AMCs with ester functionality[a].

Entry	BH acetates (**1**)	Active methylene compounds (**2**)	Product[b] (**3**)	Time (h)	Yield (%)[c]
a				2	93
b				4	66
c				3	82
d				2	89
e				3	77
f				3	70
g				4	68
h				4	64
i				4	56
j				1	83
k				2	78

[a]All reactions were performed using BH acetate (1.0 mmol, 1.0 equiv.), Active methylene compounds (1.5 equiv.) and DBU (1.2 equiv.) at room temperature

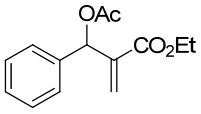
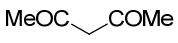
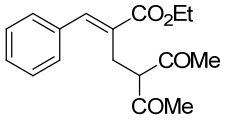
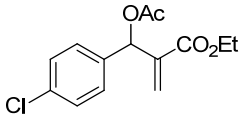
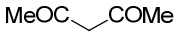
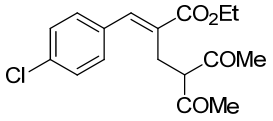
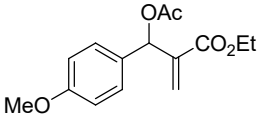
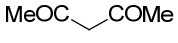
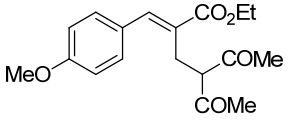
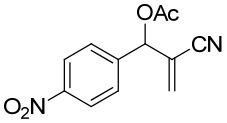
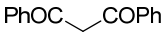
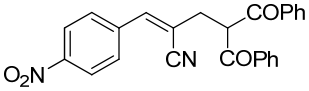
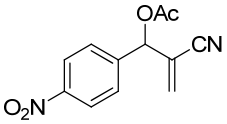
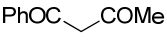
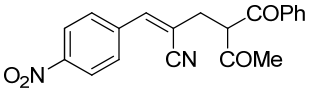
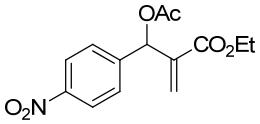
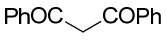
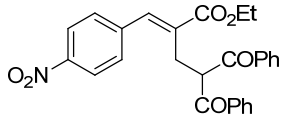
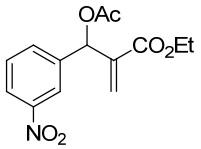
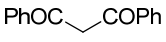
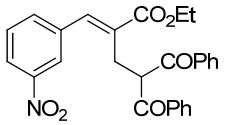
[b]Products were characterized by NMR, IR and mass spectrometry

[c]Yield refers to pure product after chromatography

Accordingly, we used other Baylis-Hillman acetates synthesized from substituted benzaldehyde such as 4-chlorobenzaldehyde (**1e**, **1f** and **1m**), 4-methoxybenzaldehyde (**1g-1i** and **1n**), 4-nitrobenzaldehyde (**1j**, **1k** and **1o-1q**) and 3-nitrobenzaldehyde (**1r**) with ethyl acrylate or acrylonitrile. Active methylene compounds having ester group such as diethyl malonate (**2a**, **2d**, **2e**, **2g** and **2j**), ethyl cyanoacetate (**2b**, **2i** and **2k**) and ethyl acetoacetate (**2c**, **2f** and **2h**) under optimized reaction condition gave the desired tri-substituted olefins in good to excellent yields with high stereoselectivity *i.e.* *E*-isomer in case of Baylis-Hillman adducts derived from acrylate ester and *Z*- isomer in case of Baylis-Hillman adducts derived from acrylonitrile (Table 2). The stereoselectivity of nucleophilic substitution reactions at allylic carbon of Baylis-Hillman acetates are well known in the literature[42-44]. The stereochemistry of the products was confirmed by comparing the signal of the vinylic methylene proton in ^{1}H NMR spectra which matched with the reported values[30,45]. The peak for the vinylic methylene proton of the *E*-isomer appears at around δ =7.8 ppm whereas, for the *Z*-isomer, the peak appeared around δ = 7.1 ppm in ^{1}H NMR spectra. Baylis-Hillman acetates derived from benzaldehyde (**1a-1d** and **1l**) and substituted benzaldehyde with electron donating group (EDG, **1e-1i** and **1m**, **1n**) was found to be equally effective.

However, 1,3-diketones such as acetylacetone (**2l-2n**), benzoyl acetone (**2p**) and dibenzoylmethane (**2o**, **2q** and **2r**) gave the similar product *i.e.* tri-substituted alkenes in good yields with high stereoselectivity (Table 3). It is observed that

Table 3 — Synthesis of diversified tri-substituted alkenes by reaction of BH acetates with 1,3-diones[a]

Entry	BH acetates (**1**)	Active methylene compounds (**2**)	Product[b] (**3**)	Time (h)	Yield (%)[c]
l				3	74
m				3	75
n				4	72
o				2	88
p				2	85
q				1	90
r				1	79

[a]All reactions were performed using BH acetate (1.0 mmol, 1.0 equiv.), Active methylene compounds (1.5 equiv.) and DBU (1.2 equiv.) at room temperature

[b]Products were characterized by NMR, IR and mass spectrometry

[c]Yield refers to pure product after chromatography

Baylis-Hillman acetates prepared from substituted benzaldehyde with electron-withdrawing group (EWG, **1j**, **1k** and **1o-1r**) were found to be more reactive and gave good yields in shorter reaction time. This different reactivity may be attributed because of the decrease in electrophilicity of vinylic carbon of Baylis-Hillman acetates derived from substituted benzaldehyde with electron donating group (EDG).

Conclusions

In conclusion, we describe an efficient and facile method for the stereoselective synthesis of tri-substituted olefins from Baylis-Hillman acetates and active methylene compounds using DBU as unique base at room temperature under neat condition. The resultant tri-substituted can be utilized for the synthesis of various O-heterocycles like γ-lactones and δ-lactones.

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Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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