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The first application of the Baylis–Hillman reaction in azetidine chemistry: a convenient synthesis of azetidine-3-carbonitriles/carboxylates

Lal Dhar S. Yadav *, Vishnu P. Srivastava, Rajesh Patel

Green Synthesis Laboratory, Department of Chemistry, University of Allahabad, Allahabad 211 002, India

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ABSTRACT

The first application of Baylis–Hillman adducts in the synthesis of azetidines is reported. The synthesis involves a one-pot, high yielding and highly diastereoselective annulation of unmodified Baylis–Hillman adducts with *N*-arylphosphoramidates to afford 1,2-disubstituted azetidine-3-carbonitriles/carboxylates, which are the precursors of biologically versatile azetidine-3-carboxylic acids.

Azetidines constitute an important class of compounds because of their interesting pharmacological activities and synthetic utility. Whereas the strain associated with the azetidine ring system leads to difficulties in its synthesis, functionalization and modification, it is advantageous for its synthetic applications involving ring-opening reactions. Over the past few years, several functionalized azetidines have been utilized as masked 1,4-dipoles for the construction of five- and six-membered azaheterocycles.[1]

L-Azetidine-2-carboxylic acid (L-Aze) is the first known example of a naturally occurring azetidine,[2] and it has shown some unique and potentially useful biological activity.[3] Following this first discovery, many natural products such as mugineic acid,[4] 2′-deoxymugineic acid,[5] nicotianamine,[6] medicanine,[7] antifungal and antibiotic polyoxins,[8] substituted azetidine-2,4-dicarboxylic acids,[9] and pharmacologically important molecules such as thrombin inhibitors melagatran and exenta[10] have been reported to incorporate L-Aze in their structure. As a constrained α-amino acid, L-Aze has found many applications in the modification of peptide conformations[11] and in asymmetric synthesis.[12]

Owing to the greater hydrolytic stability of β-amino acid derivatives, they are advantageous over α-amino acid derivatives. Thus, azetidine-3-carboxylic acid, a constrained β-amino acid isomeric to L-Aze, has also been used for the preparation of a variety of pharmaceutically active compounds, including CCR5 receptor modulators, procollagen C-proteinase inhibitors, tryptase inhibitors, IL-5 inhibitors, growth hormone secretagogues and others.[13] Several methods for the synthesis of azetidine-3-carboxylic acid and its 1-/1,2-disubstituted analogues are available in the literature.[14] However, all of these reported methods involve multistep synthetic operations, and the starting materials are not so readily available. Thus, a convenient synthesis of new 1,2-disubstituted azetidine-3-carboxylic acids, the target of present investigation, is interesting from both chemical and pharmacological viewpoints.

The Baylis–Hillman reaction is a synthetically useful and atom-economical carbon–carbon bond forming reaction yielding functionalized allylic alcohols, thereby providing handles for further manipulation in a multitude of synthetic organic transformations. Baylis–Hillman (BH) adducts incorporate three chemospecific groups, viz. a hydroxyl group, a double bond and an electron-withdrawing group (EWG). These groups can be tailored appropriately to generate an array of cyclic scaffolds directly from the BH adducts. Very recently, an excellent review has covered applications of BH adducts in the synthesis of cyclic frameworks.[15] However, until now, BH adducts have not been used for the synthesis of azetidines.

Considering the above points and our ongoing efforts to develop new convenient cyclization processes,[16] we report herein a one-pot synthetic protocol for hitherto unknown azetidine-3-carbonitriles/carboxylates utilizing BH adducts as the substrate. The carbonitriles/carboxylates thus obtained could be easily hydrolyzed into the target azetidine-3-carboxylic acids.[17,18] Initially, we tried a one-pot sequential reaction involving the aza-Michael addition of the anion **3** of phosphoramidate **2** to acrylonitrile/methyl acrylate

* Corresponding author. Tel.: +91 5322500652; fax: +91 5322460533.
E-mail address: ldsyadav@hotmail.com (L. D. S. Yadav).

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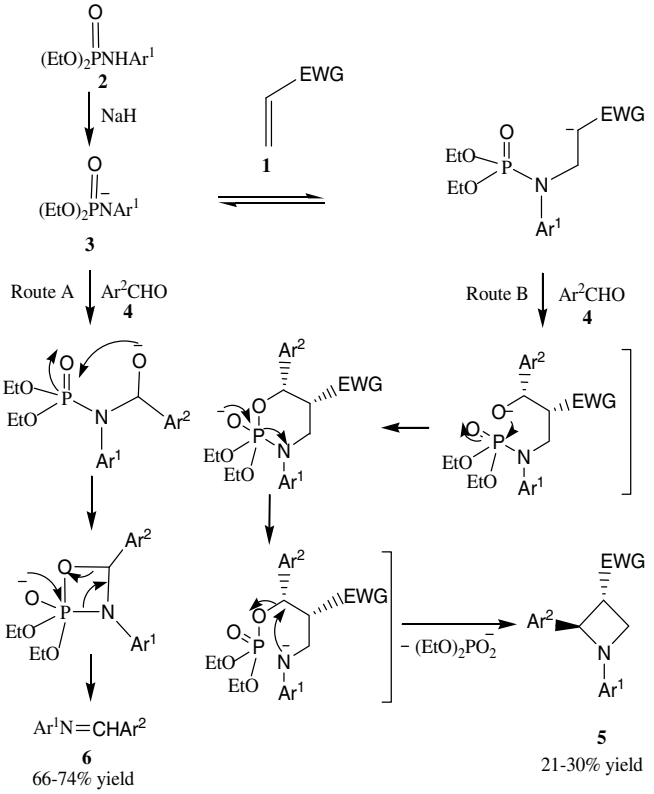
followed by addition–cyclization with aldehyde **4**. However, the corresponding functionalized azetidines **5** were obtained in only 21–30% yields (Scheme 1, Route B). The major products of the reaction were the Schiff bases **6** formed in 66–74% yields (Scheme 1, Route A). In order to improve the yield of azetidines **5**, we turned our attention to combine aldehyde **4** and acrylonitrile/methyl acrylate **1** via the BH reaction followed by cyclization of the resulting BH adduct **7** to the corresponding azetidines **5** in a one-pot procedure (Scheme 2). Fortunately, this procedure worked well and the desired azetidines **5** were obtained in high yields (84–93%) without formation of the Schiff base **6** in any appreciable amount. The requisite BH adducts **7** were prepared employing the known method.[19]

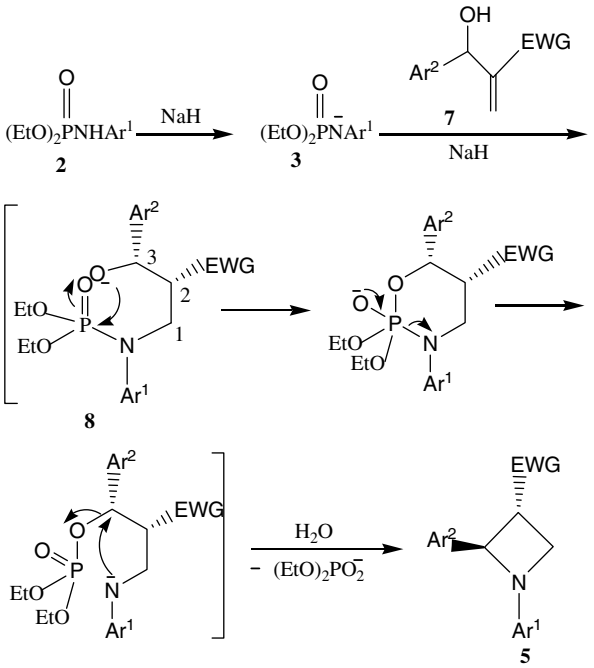
In the present one-pot procedure, diethyl *N*-arylphosphoramidates **2** were treated with sodium hydride in dry benzene to generate anion **3** in situ, which underwent aza-Michael addition to BH adducts **7** followed by cyclization of adduct **8** to afford the azetidine-3-carbonitriles/carboxylates **5** in 84–93% yields (Table 1).[20] The formation of azetidines **5** is best explained through intramolecular attack of the alkoxide ion **8** on the phosphorus atom (Scheme 2). The representative alkoxides **8a** ($Ar^1 = Ar^2 = Ph$, EWG = CN) and **8g** ($Ar^1 = Ar^2 = Ph$, EWG = COOMe) could be isolated as their parent alcohols **9a** and **9g** in 42–51% yields, which could be easily converted into the corresponding azetidines **5a** and **5g** in 94–96% yields under the same reaction conditions.[21] The high affinity of phosphorus for oxygen is the main driving force for the present cyclization reaction.

The annulation of BH adducts **7** to functionalized azetidines **5** was highly diastereoselective and afforded exclusively the trans isomers **5**. The trans stereochemistry of azetidines **5** was assigned on the basis of the ^{1}H NMR spectra by comparison of the *J* values of 2-H and 3-H with very similar 1,2-disubstituted azetidine-3-carbonitriles/carboxylates reported in the literature,[22] whose configuration had already been confirmed by X-ray crystallographic studies.[17] Furthermore, the absence of any measurable NOE between 2-H and 3-H indicates that these protons are on opposite faces of the molecule.

In summary, we have developed a one-pot procedure for a highly diastereoselective synthesis of 1,2-disubtituted azetidine-3-carbonitriles/carboxylates which are precursors of 3-carboxylic acid analogues via annulation of BH adducts with *N*-arylphosphoramidates. This synthetic protocol presents the first application of the BH reaction in the field of azetidines.

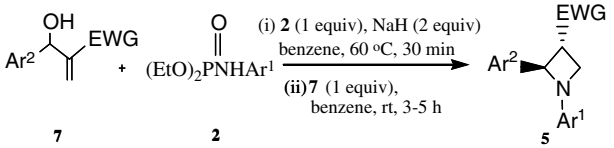


Scheme 1. A plausible mechanism for the formation of azetidines **5** from aldehyde **4** and activated alkene **1**.



Scheme 2. A plausible mechanism for the formation of azetidines **5** from BH adducts **7**.

Table 1
Synthesis of functionalized azetidines **5**



Compound	Ar^1	Ar^2	EWG	Time[a] (h)	Yield[b,c] (%)
5a	Ph	Ph	CN	4	87
5b	Ph	4-$O_2NC_6H_4$	CN	4	89
5c	Ph	4-$C1C_6H_4$	CN	5	85
5d	4-$CH_3C_6H_4$	Ph	CN	4	88
5e	4-$CH_3C_6H_4$	4-$O_2NC_6H_4$	CN	3	93
5f	4-$CH_3C_6H_4$	4-$C1C_6H_4$	CN	5	89
5g	Ph	Ph	COOMe	5	84
5h	Ph	4-$O_2NC_6H_4$	COOMe	4	87
5i	Ph	4-$C1C_6H_4$	COOMe	5	84
5j	4-$CH_3C_6H_4$	Ph	COOMe	4	86
5k	4-$CH_3C_6H_4$	4-$O_2NC_6H_4$	COOMe	3	91
5l	4-$CH_3C_6H_4$	4-$C1C_6H_4$	COOMe	5	90

[a] Time required for completion of step (ii).
[b] Yield refers to pure products after column chromatography.
[c] All compounds gave C, H and N analyses within ±0.36% and satisfactory spectral (IR, ^{1}H NMR, ^{13}C NMR and EIMS) data.

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20. *General procedure for the synthesis of azetidine-3-carbonitriles/carboxylates* **5**: To a solution of diethyl *N*-arylphosphoramidate **2** (5 mmol) in dry benzene (5 mL) was added dropwise a suspension of NaH (240 mg, 10 mmol) in dry benzene (20 mL) with stirring at rt. After the addition was complete and evolution of hydrogen gas (effervescence) had ceased, the reaction mixture was stirred at 60 °C for 30 min and then cooled to rt. Next, a solution of Baylis–Hillman adduct **7** (5 mmol) in dry benzene (5 mL) was added, and the reaction mixture was stirred at rt for 3–5 h (Table 1). Water (30 mL) was added, the mixture was extracted with ether (3 × 30 mL), the combined organics were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure. The crude product thus obtained was purified by silica gel column chromatography (hexane/EtOAc, 95:5) to afford an analytically pure sample of **5**. Physical data of representative compounds. Compound **5a**: Colourless syrup, yield 87%. IR (film): ν 3010, 2975, 2925, 2875, 2245, 1495, 1453, 1100, 752, 700 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ = 3.67 (ddd, 1H, J = 8.8, 7.2, 2.9 Hz, 3-H), 4.01 (dd, 1H, J = 11.2, 7.2 Hz, 4-H_a), 4.16 (dd, 1H, J = 11.2, 2.9 Hz, 4-H_b), 4.96 (d, 1H, J = 8.8 Hz, 2-H), 7.11-7.41 (m, 10$H_{arom.}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ = 50.1 (3-C), 57.5 (4-C), 71.0 (2-C), 119.6 (CN), 126.6, 127.5, 128.3, 129.3, 130.7, 131.7, 136.1, 141.0 ($C_{arom.}$). EIMS (m/z): 234 (M^+). Anal. Calcd for $C_{16}H_{14}N_2$: C, 82.02; H, 6.02; N, 11.96. Found: C, 82.38; H, 6.28; N, 11.67.
Compound **5g**: Colourless syrup, yield 84%. IR (film): ν 3000, 2972, 2928, 2879, 1750, 1593, 1492, 1104, 755, 706 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$/TMS): δ = 3.54 (ddd, 1H, J = 8.9, 7.1, 3.0 Hz, 3-H), 3.65 (s, 3H, OMe), 3.82 (dd, 1H, J = 12.1, 7.1 Hz, 4-H_a), 3.96 (dd, 1H, J = 12.1, 3.0 Hz, 4-H_b), 5.25 (d, 1H, J = 8.9 Hz, 2-H), 7.10–7.34 (m, 10$H_{arom.}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ = 41.1 (3-C), 51.5 (OCH_3), 57.0 (4-C), 69.9 (2-C), 126.0, 127.6, 128.2, 129.3, 130.5, 131.5, 135.8, 141.0 ($C_{arom.}$), 172.0 (C═O). EIMS (m/z): 267 (M^+). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.05; H, 6.11; N, 5.55.
21. *General procedure for the isolation of alkoxides* **8a** *(Ar^1 = Ar^2 = Ph, EWG = CN) and* **8g** *(Ar^1 = Ar^2 = Ph, EWG = COOMe) as their parent alcohols* **9a** *and* **9g** *and their conversion into the corresponding azetidines* **5a** *and* **5g**: The procedure followed was the same as described above[20] for the synthesis of **5** except that the time of stirring at rt was 2 h instead of 3–5 h for **5**. The alcohols **9a** and **9g** were obtained with *syn* stereoselectivity. Their *syn* stereochemistry was assigned on the basis of ^1H NMR spectra and literature precedent.[23] A mixture of NaH (48 mg, 2 mmol) and **9a** or **9g** (2 mmol) was stirred at rt in dry benzene (15 mL) for 4 h. The product **5a** or **5g** was isolated in 96% or 94% yield, respectively, following the same work up procedure as described above for **5**.[20] Physical data of representative compounds.
Compound **9a**: IR (KBr): ν 3455, 3052, 2990, 2241, 1605, 1582, 1456, 745, 703 cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$ + D_2O/TMS): δ = 1.23 (t, 6H, J = 7.5 Hz, 2 × Me), 3.25 (ddd, 1H, J = 6.2, 4.8, 3.2 Hz, 2-H), 3.42 (dd, 1H, J = 12.1, 6.2 Hz, 1-H_a), 3.56 (dd, 1H, J = 12.1, 3.2 Hz, 1-H_b), 4.16 (q, 4H, J = 7.5 Hz, 2 × CH_2), 4.85 (d, 1H, J = 4.8 Hz, 3-H), 7.08–7.43 (m, 10$H_{arom.}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ = 16.3 (Me), 43.5 (CH_2N), 49.5 (CHCN), 50.3 (CH_2O), 72.3 (CHOH), 120.1 (CN), 126.7, 127.8, 131.6, 133.5, 134.6, 136.2, 140.5, 148.0 ($C_{arom.}$). EIMS (m/z): 388 (M^+). Anal. Calcd for $C_{20}H_{25}N_2O_4P$: C, 61.85; H, 6.49; N, 7.21. Found: C, 61.56; H, 6.73; N, 7.42.
Compound **9g**: IR (KBr): ν 3452, 3050, 2983, 1695, 1602, 1580, 1453, cm^{-1}. ^1H NMR (400 MHz; $CDCl_3$ + D_2O/TMS): δ = 1.22 (t, 6H, J = 7.5 Hz, 2 × Me), 3.10 (ddd, 1H, J = 6.7, 4.7, 3.1 Hz, 2-H), 3.35 (dd, 1H, J = 11.6, 6.7 Hz, 1-H_a), 3.45 (dd, 1H, J = 11.6, 3.1 Hz, 1-H_b), 3.64 (s, 3H, OMe), 4.15 (q, 4H, J = 7.5 Hz, 2 × CH_2), 5.08 (d, 1H, J = 4.7 Hz, 3-H), 7.01–7.34 (m, 10$H_{arom.}$). ^{13}C NMR (100 MHz; $CDCl_3$/TMS): δ = 16.3 (Me), 46.4 (CH_2N), 48.2 (OMe), 50.3 (CH_2O), 54.2 (*C*HC═O), 71.1 (CHOH), 126.5, 127.5, 131.3, 133.7, 134.5, 136.2, 140.3, 148.0 ($C_{arom.}$). EIMS (m/z): 421 (M^+). Anal. Calcd for $C_{21}H_{28}NO_6P$: C, 59.85; H, 6.70; N, 3.32. Found: C, 60.21; H, 6.49; N, 3.58.
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