A Simple and Direct Synthesis of 3-Methylene-1, 4-diarylazetidin-2-ones and (E)-3-Arylidene-1-phenylazetidin-2-ones Using Baylis–Hillman Derivatives

Manickam Bakthadoss, A,B,C Jayakumar Srinivasan, B and Raman Selvakumar B

A Department of Chemistry, Pondicherry University, Puducherry 605 014, India.
B Department of Organic Chemistry, University of Madras, Guindy Campus, Chennai 600 025, India.
C Corresponding author. Email: bhakthadoss@yahoo.com

Herein we describe a direct method, promoted by potassium tert-butoxide (KOtBu), for the synthesis of highly substituted α-methylene β-lactams and α-arylidene β-lactams from the amino ester intermediates derived from the acetates and bromo derivatives of the Baylis–Hillman adducts. A variety of β-lactams was synthesized in a single step with good yields.

Introduction
The β-lactam moiety is an important integral part of many natural products and biologically active molecules, the latter being mostly antibiotics and serine protease inhibitors.[1] Penicillins, carbapenems, cephalosporins, and monobactams are some of the β-lactam core-containing antibacterials which have been used therapeutically to date (Fig. 1). Apart from clinical use, β-lactams can also serve as good synthons in the synthesis of many biologically active heterocycles.[2]

In recent years, the Baylis–Hillman reaction has emerged as a powerful synthetic tool for the synthesis of diverse classes of multifunctional molecules.[3] Baylis–Hillman adducts can be used as synthons to obtain a wide variety of natural products and biologically active molecules.[4] We have been working on the application of Baylis–Hillman adducts[5] with a view to demonstrate that Baylis–Hillman chemistry is a powerful tool for the synthesis of various important and useful structural frameworks. Due to the multifunctionality present in Baylis–Hillman adducts, the opportunity for converting them into a new class of cyclic compounds is high and is very attractive in the field of organic chemistry. Although Baylis–Hillman adducts have been utilised for numerous applications,[6] the transformation of Baylis–Hillman adducts into β-lactam is very limited.[7] All the literature methods available for the formation of β-lactams involves lactamization, achieved by the coupling of amino and ester groups which is a two step process: the ester group is hydrolyzed to an acid moiety followed by the coupling of acid and amino groups in an intramolecular fashion to obtain the β-lactam core moiety.

Results and Discussion
We envisaged that an amino group and ester moiety could be directly cyclized using potassium tert-butoxide (KOtBu) without hydrolyzing the ester group. Therefore, we planned to directly connect the ester moiety and amino group (which is present in the β-position) in an intramolecular fashion using KOtBu in a shorter synthetic sequence to obtain α-methylene β-lactam 4 from the amino ester 3 (Table 1). We also envisage that the α-arylidene β-lactam 7 can be easily achieved from the amino ester 6 (Table 2). According to the retro-synthetic strategy, Baylis–Hillman adducts can be easily converted into the corresponding substituted amino ester 3 by an SN2 reaction. The amino ester 3 can be easily converted into the corresponding α-methylene β-lactam 4 by direct intramolecular cyclization. Similarly, the amino ester 6 can be easily synthesized from the bromo derivative of Baylis–Hillman adducts by an SN2 reaction, and a direct lactamization of an amino group with an ester group in an intramolecular fashion will lead to the desired α-arylidene β-lactam 7 core as described in Scheme 1.

![Fig. 1. β-Lactam antibacterials currently in use.](image-url)
Table 1. Synthesis of \(\alpha\)-methylene \(\beta\)-lactams 4a–j from methyl 2-(aryl (phenylamino)methyl)acrylates 3a–j

Lactamization was performed using K\textsubscript{Bu} as a base in single step.

\[ \text{R}_1 = \text{H}, \text{4-Me}, \text{4-Et}, \text{4-Propyl}, \text{4-Cl}, \text{4-F} \]
\[ \text{R}_2 = \text{H, Me} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amino ester intermediates(^\text{A})</th>
<th>Yield(^\text{B}) [%]</th>
<th>(\beta)-Lactam products(^\text{B})</th>
<th>Yield(^\text{C, D}) [%]</th>
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(continued)
Synthesis of β-lactams

To execute our idea, we first selected methyl 2-(acetoxy(phenyl)methyl)acrylate (2a), and treated it with 1,4-diazabicyclo[2.2.2]octane (DABCO) in THF at room temperature for 15 min which led to the DABCO salt of Baylis–Hillman acetate. To this DABCO salt, aniline was added and stirred at room temperature for 1 h which successfully furnished the desired amino ester (3a) in 76 % yield. Further treatment of amino ester 3a with KO\textsubscript{t-Bu} in dry THF at 0°C for 1 h successfully led to the desired β-lactam, i.e. 3-methylene-1,4-diphenylazetidin-2-one (4a) in 66 % yield (Entry 1, Table 1). Encouraged by this result, we prepared a variety of amino esters using anilines 3b–f and treated them with KO\textsubscript{t-Bu} which successfully led to the anticipated substituted 3-methylene β-lactams 4b–f in 65–70 % yields (Entries 2–6, Table 1). To further extend the methodology, we also employed p-toluidine for the lactamization reaction. Reaction of methyl 2-(acetoxy(aryl)methyl)acrylates 2a, 2b, 2d, and 2e, with DABCO in THF for 15 min led to the corresponding DABCO salts. To these DABCO salts, p-toluidine was added and the mixture stirred at room temperature for 1 h which led to the anticipated amino esters 3g–j in 72–83 % yields. Further treatment of amino ester precursors 3g–j with KO\textsubscript{t-Bu} successfully provided the desired products, i.e. 3-methylene-4-aryl-1-p-tolylazetidin-2-ones 4g–j in 66–71 % yields (Entries 7–10, Table 1).

After successfully synthesizing an array of 3-methylene-1,4-diaryiazetidin-2-ones (4a–j), we planned to utilise the same protocol for the synthesis of (E)-3-benzylidene-1-phenylazetidin-2-one (7a) from (E)-methyl 2-(phenylamino)methyl)-3-phenylacrylate (6a).

Treatment of (Z)-methyl 2-(bromomethyl)-3-phenylacrylate (5a) with anilines in the presence of potassium carbonate in CH\textsubscript{3}CN for 3 h led to the formation of required amino ester precursor 6a in 79 % yield. The amino ester 6a was further treated with KO\textsubscript{t-Bu} in dry THF at 0°C for 1 h which successfully led to the desired (E)-3-benzylidene-1-phenylazetidin-2-one (7a) in 65 % yield (Entry 1, Table 2). Encouraged by this result, we prepared a variety of amino ester precursors 6b–f and treated them with KO\textsubscript{t-Bu} which smoothly led to the desired substituted α-arylidene β-lactams 7b–f in 63–72 % yields (Entries 2–6, Table 2).

Conclusion

In conclusion, we have successfully developed a first general method for the synthesis of both α-methylene β-lactams and α-arylidene β-lactams in a single step with good yields using Baylis–Hillman adducts. Comparatively, this method is very simple and better than the methods already known in the literature. Since the core unit of β-lactam is an integral part of many biologically active molecules, the derivatives which we have synthesized may also possess similar activity which will be studied in our laboratory in the future.

Experimental

All reagents were purchased from commercial sources and used without further purification. Solvents were distilled before use. Column chromatography was performed on silica gel. IR spectra were recorded on an FTIR-8300 Shimadzu spectrophotometer. \textsuperscript{1}H NMR (300 MHz) and \textsuperscript{13}C NMR (75 MHz) spectra were recorded on a Bruker spectrometer using CDCl\textsubscript{3} as solvent and tetramethylsilane as an internal standard; chemical shifts are reported in δ (ppm). Mass spectra were recorded on a Jeol-JMS-DX 303 HF mass spectrometer. Elemental analyses were recorded on a Perkin–Elmer 240C CHN analyzer. Melting points are uncorrected. Thin-layer chromatography (TLC) was performed using glass plates coated with silica gel (ACME, 254F). Spots were visualized using iodine vapour and UV lamp. Methyl 2-([phenyl](phenylamino)methyl)acrylate (3a): Typical Procedure

To a stirred solution of methyl 2-(acetoxy(phenyl)methyl) acrylate (2a) (1.17 g, 5 mmol) in THF (8 mL), DABCO (0.56 g, 5 mmol) was added and stirred at room temperature for 15 min. To this solution aniline (0.47 g, 5 mmol) was added and stirred for 1 h at room temperature. After completion of the reaction, as monitored by TLC, the reaction mixture was evaporated under vacuum, the residue was purified by column chromatography (AcOEt/hexane 9:1) to afford the desired product 3a as white solid in 71 % yield.

Table 1. (Continued)

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<th>Yield\textsuperscript{b, c} [%]</th>
<th>β-Lactam products\textsuperscript{b}</th>
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\textsuperscript{a}All reactions were carried out using 5 mmol of acetates 2a–f.

\textsuperscript{b}All the reactions were carried out using 2.5 mmol of amino esters 3a–j with 2.5 mmol of potassium tert-butoxide in dry THF (10 mL) for 1 h at 0°C.

\textsuperscript{c}Yields of the pure products 3a–j and 4a–j obtained after column chromatography.

\textsuperscript{d}All the products gave satisfactory IR, \textsuperscript{1}H and \textsuperscript{13}C NMR, and mass spectra.
Table 2. Synthesis of \( \alpha \)-arylidene \( \beta \)-lactams 7a–f from (E)-methyl 2-((phenylamino)methyl)-3-arylacrylates 6a–f

Lactamization was performed using KO\textsubscript{t}Bu as a base in single step.

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<th>Entry</th>
<th>Amino ester intermediates(^a)</th>
<th>Yield(^c) [%]</th>
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\(^a\)All the reactions were carried out using 5 mmol of bromo derivatives (5a–f).
\(^b\)All the reactions were carried out using 2.5 mmol of amino esters (6a–f) with 2.5 mmol of potassium tert-butoxide in dry THF (10 mL) for 1 h at 0°C.
\(^c\)Yields of the pure products 6a–f and 7a–f obtained after column chromatography.
\(^d\)All the products gave satisfactory IR, \(^1\)H and \(^13\)C NMR, and mass spectra.

Reduced pressure to remove THF. The crude mixture obtained was diluted with water (10 mL) and extracted with ethyl acetate (3 \( \times \) 10 mL). The combined organic layers were dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure which led to the crude product. The crude product thus obtained was purified by column chromatography (with 4% ethyl acetate in hexanes) to afford the methyl 2-(phenyl(phenylamino)methyl)acrylate (3a) as a colourless liquid.

**Methyl 2-(Phenyl(phenylamino)methyl)acrylate (3a)**

Yield: 76%. Reaction time: 1 h. \( \delta \text{H} = 3.71 \) (s, 3H), 4.15 (br s, 1H), 5.42 (s, 1H), 5.97 (s, 1H), 6.39 (s, 1H), 6.56–7.39 (m, 10H). \( \delta \text{C} = 51.90, 58.99, 113.48, 117.94, 126.18, 127.52, 127.81, 128.77, 129.18, 140.13, 140.66, 146.70, 166.68. \( \nu \text{max} \) (KBr)/cm\(^{-1}\) = 3389.35, 1714.64, 1629.58.

3-Methylene-1,4-diphenylazetidin-2-one (4a): Typical Procedure

To a stirred solution of methyl 2-(phenyl(phenylamino)methyl)acrylate (3a) (0.67 g, 2.5 mmol) in dry THF (10 mL), KO\textsubscript{t}Bu (0.37 g, 2.5 mmol) was added at 0°C. The reaction mixture was stirred for one hour at 0°C and then THF was removed under reduced pressure. The crude product thus obtained was diluted with water (10 mL) and extracted with ethyl acetate (3 \( \times \) 10 mL). The combined organic layers were washed with brine solution and dried over anhydrous Na\textsubscript{2}SO\textsubscript{4},
Solvent was evaporated under reduced pressure and the crude product thus obtained was purified by column chromatography (with 20% ethyl acetate in hexanes) which afforded the 3-methylene-1,4-diphenylazetidin-2-one (4a) as a colourless solid.

3-Methylene-1,4-diphenylazetidin-2-one (4a)

Yield: 66%. Reaction time: 1 h. Mp 121–123°C. δH (300 MHz, CDCl3) 5.31 (s, 1H), 5.98 (s, 1H), 6.45–7.29 (m, 11H). δC (75 MHz, CDCl3) 58.65, 113.57, 118.16, 127.59, 127.95, 128.68, 128.84, 129.23, 139.55, 140.35, 146.52, 171.38. Anal. Calc. for C16H13NO: C 81.68, H 5.57, N 5.95. Found: C 81.61, H 5.49, N 5.08 %.

3-Methylene-1-phenyl-4-p-tolyiazetidin-2-one (4b)

Yield: 67%. Reaction time: 1 h. Mp 136–138°C. δH (300 MHz, CDCl3) 2.33 (s, 3H), 5.34 (s, 1H), 6.04 (s, 1H), 6.51–7.25 (m, 10H). δC (75 MHz, CDCl3) 21.14, 58.35, 113.53, 118.06, 127.55, 128.43, 129.23, 129.54, 137.39, 137.72, 139.61, 146.58, 171.67. vmax (neat)/cm⁻¹ 1685, 1602. mz 235 (M⁺). Anal. Calc. for C16H15NO: C 81.68, H 5.57, N 5.95. Found: C 81.61, H 5.49, N 6.06 %.

4-(4-Ethylphenyl)-3-methylene-1-phenylazetidin-2-one (4c)

Yield: 70%. Reaction time: 1 h. Mp 140–142°C. δH (300 MHz, CDCl3) 1.15 (t, 3H, J 7.5), 2.56 (q, 2H, J 7.5), 5.27 (s, 1H), 6.01 (s, 1H), 6.46 (s, 1H), 6.55–7.21 (m, 9H). δC (75 MHz, CDCl3) 15.38, 28.49, 58.67, 113.81, 118.35, 126.70, 128.36, 129.21, 137.35, 139.48, 144.05, 146.26, 171.22. vmax (neat)/cm⁻¹ 1686, 1627. mz 263 (M⁺). Anal. Calc. for C19H16NO: C 81.95, H 6.12, N 5.59 %.

4-(4-Isopropylphenyl)-3-methylene-1-phenylazetidin-2-one (4d)

Yield: 65%. Reaction time: 1 h. Mp 148–151°C. δH (300 MHz, CDCl3) 1.16 (d, 6H, J 6.9), 2.82 (sep, 1H, J 6.9), 5.26 (s, 1H), 6.01 (s, 1H), 6.52 (s, 1H), 6.70–7.26 (m, 9H). δC (75 MHz, CDCl3) 23.95, 33.80, 58.32, 113.50, 118.03, 126.91, 127.57, 128.41, 129.22, 137.64, 139.54, 146.57, 146.64, 171.71. vmax (neat)/cm⁻¹ 1683, 1625. mz 277 (M⁺). Anal. Calc. for C20H20NO: C 82.28, H 6.90, N 5.05. Found: C 82.32, H 6.95, N 5.08 %.

4-(4-Chlorophenyl)-3-methylene-1-phenylazetidin-2-one (4e)

Yield: 68%. Reaction time: 1 h. Mp 152–154°C. δH (300 MHz, CDCl3) 5.27 (s, 1H), 6.01 (s, 1H), 6.58 (s, 1H), 6.86–7.35 (m, 9H). δC (75 MHz, CDCl3) 58.09, 113.61, 118.43, 128.89, 128.99, 129.10, 129.27, 133.78, 138.87, 154.29, 146.27, 170.91. vmax (neat)/cm⁻¹ 1684, 1600. mz 269 (M⁺). Anal. Calc. for C16H12ClNO: C 71.25, H 4.48, N 5.19. Found: C 71.21, H 4.43, N 5.23.

4-(4-Fluorophenyl)-3-methylene-1-phenylazetidin-2-one (4f)

Yield: 69%. Reaction time: 1 h. Mp 158–160°C. δH (300 MHz, CDCl3) 5.29 (s, 1H), 5.98 (s, 1H), 6.46–7.28 (m, 10H). δC (75 MHz, CDCl3) 58.06, 113.72 (d, J 66), 115.96, 115.85, 116.14, 118.46 (d, J 69), 129.28, 131.90 (d, J 36), 143.96, 146.36, 147.37, 172.47. vmax (neat)/cm⁻¹ 1232, 1592, 1627, 1697, 3254. mz 253 (M⁺). Anal. Calc. for C16H12FNO: C 75.88, H 4.78, N 5.53. Found: C 75.93, H 4.71, N 5.61 %.

3-Methylene-4-phenyl-1-p-tolyiazetidin-2-one (4g)

Yield: 67%. Reaction time: 1 h. Mp 126–128°C. δH (300 MHz, CDCl3) 2.23 (s, 3H), 5.24 (s, 1H), 5.94 (s, 1H), 6.40–7.14 (m, 10H). δC (75 MHz, CDCl3) 20.01, 57.27, 112.45, 116.98, 126.42, 127.31, 128.12, 128.42, 136.30, 136.60, 138.54, 145.48, 170.64. vmax (neat)/cm⁻¹ 1237, 1592, 1635, 1717, 3284. mz 249 (M⁺). Anal. Calc. for C17H16NO: C 81.90, H 6.06, N 5.62. Found: C 81.86, H 6.09, N 5.68 %.

3-Methylene-1,4-dip-tolyiazetidin-2-one (4h)

Yield: 68%. Reaction time: 1 h. Mp 134–136°C. δH (300 MHz, CDCl3) 2.23 (s, 3H), 2.33 (s, 3H), 5.29 (s, 1H), 6.02 (s, 1H), 6.48–7.25 (m, 9H). δC (75 MHz, CDCl3) 20.38, 21.09, 58.79, 113.78, 127.43, 127.47, 128.33, 129.48, 129.70, 137.49, 137.64, 139.72, 144.24, 171.16. vmax (neat)/cm⁻¹ 1234, 1486, 1621, 1700, 3381. mz 263 (M⁺). Anal. Calc. for C18H17NO: C 82.10, H 6.51, N 5.32. Found: C 82.14, H 6.48, N 5.27 %.

4-(4-Isopropylphenyl)-3-methylene-1-p-tolyiazetidin-2-one (4i)

Yield: 71%. Reaction time: 1 h. Mp 155–157°C. δH (300 MHz, CDCl3) 1.24 (d, 6H, J 6.9), 2.23 (s, 3H), 2.89 (sep, 1H, J 6.9), 5.31 (s, 1H), 6.03 (s, 1H), 6.49–7.28 (m, 9H). δC (75 MHz, CDCl3) 20.37, 23.90, 33.76, 59.00, 113.90, 126.86, 127.45,
128.30, 129.70, 130.18, 137.98, 139.60, 144.02, 148.43, 170.26.

\( v_{\text{max}} \) (neat)/cm\(^{-1}\): 1236, 1485, 1594, 1706, 3436. m/z 291 (M\(^+\)). Anal. Calc. for C\(_2\)H\(_2\)NO: C 82.44, H 7.26, N 4.81. Found: C 82.38, H 7.31. N 4.87 %.

**4-(4-Chlorophenyl)-3-methylene-1-\( \rho \)-tolylazetidin-2-one (4j)**

Yield: 66 %. Reaction time: 1 h. Mp 160–162°C. \( \delta_H \) (300 MHz, CDCl\(_3\)) 2.23 (s, 3H), 5.32 (s, 1H). \( \delta_C \) (75 MHz, CDCl\(_3\)) 20.38, 58.46, 113.83, 127.75, 129.57, 131.03, 134.48, 145.00, 147.46, 172.13. \( \nu_{\text{max}} \) (KBr)/cm\(^{-1}\): 1242, 1511, 1630, 1711, 3244, m/z 249 (M\(^+\)). Anal. Calc. for C\(_1\)_\(_2\)H\(_2\)NO: C 81.90, H 6.06, N 5.62. Found: C 81.92, H 6.09, N 5.58 %.

**E)-Methyl 2-\((\text{Phenylamino})\)methyl-3-phenylacrylate (6a): Typical Procedure**

To a stirred solution of aniline (0.47 g, 5 mmol) in dry CH\(_2\)CN (15 mL), potassium carbonate (1.04 g, 7.5 mmol) was added drop wise and stirred at room temperature for 1 h. The reaction mixture was evaporated under reduced pressure which led to a yellow solid.

Yield: 79 %. Reaction time: 3 h. \( \delta_H \) 6.17 (br s, 3H), 4.13 (br s, 3H). \( \delta_C \) 41.00, 52.20, 113.47, 117.89, 128.73, 129.18, 129.25, 129.32, 129.56, 134.81, 142.88, 147.78, 168.19. \( \nu_{\text{max}} \) (KBr)/cm\(^{-1}\) 3393.60, 1717.79, 1629.58.

**E)-3-(2-Methylphenylidene)-1-phenylazetidin-2-one (7a): Typical Procedure**

To a stirred solution of (E)-2-\((\text{Phenylamino})\)methyl-3-phenylacrylate (6a) (0.67 g, 2.5 mmol) in dry THF (10 mL), KO\(_2\)Bu was added (0.37 g, 2.5 mmol) at 0°C. The reaction mixture was stirred for 1 h at 0°C and then THF was removed under reduced pressure. The crude mass obtained was diluted with water (10 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine and was dried over anhydrous Na\(_2\)SO\(_4\). Solvent was evaporated under reduced pressure and the crude product thus obtained was purified by column chromatography (15 % ethyl acetate in hexanes) which afforded the (E)-3-benzylidene-1-phenylazetidin-2-one (7a) as a yellow solid.

Yield: 65 %. Reaction time: 1 h. Mp 144–146°C. \( \delta_H \) (300 MHz, CDCl\(_3\)) 4.17 (s, 2H), 6.52–7.48 (m, 10H), 8.03 (s, 1H). \( \delta_C \) (75 MHz, CDCl\(_3\)) 41.05, 113.83, 118.40, 128.33, 128.80, 129.22, 129.63, 129.72, 134.48, 145.00, 147.46, 172.13. \( \nu_{\text{max}} \) (KBr)/cm\(^{-1}\) 1224, 1487, 1599, 1722, 1342, m/z 255 (M\(^+\)). Anal. Calc. for C\(_1\)_\(_2\)H\(_2\)NO: C 81.68, H 5.57, N 5.95. Found: C 81.72, H 5.61, N 5.91 %.

**Supplementary Material**

\(^1\)H and \(^{13}\)C NMR spectra for compounds 3a, 4a-j, 6a and 7a-f are available on the Journal’s website.

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