

Baylis–Hillman Reaction Assisted Synthesis of Substituted 5,8-Dihydroisoxazolo[4,5-*c*]azepin-4-ones: A Novel Isoxazole-Annulated Heterocycle¹

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Abstract: The novel synthesis of a new isoxazole-annulated heterocycle namely, 5,8-dihydroisoxazolo[4,5-*c*]azepin-4-one, described herein is based on the reaction of benzylamine with acetates of Baylis–Hillman adducts generated from 3-aryl-5-formyl-isoxazole-4-carboxylate.

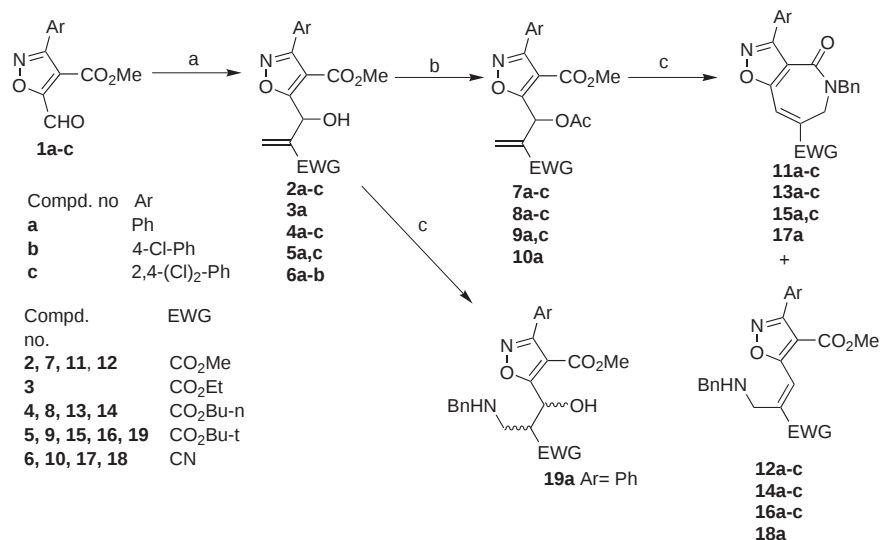
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The Baylis–Hillman reaction is extremely useful in furnishing products of high functional density and it has been extensively applied to achieve the synthesis of heterocycles and benzannulated compounds.^{2,3} These compounds have been obtained either directly as products of Baylis–Hillman reaction or by appropriate modification of derivatives of the Baylis–Hillman adducts.^{2–11}

Our research efforts are concerned with the exploration of the Baylis–Hillman reaction of substituted isoxazolecarbaldehydes and the synthetic utility of the resulting products.^{12–14} In this context we have recently reported the synthesis of 5-aryl-3-formylisoxazole-4-carboxylate.¹⁵ It occurred to us that in these compounds the presence of an electron-withdrawing group at 4-position of the isoxazole ring would not only provide a fast reacting substrate for Baylis–Hillman reaction but also would lead to a scaffold to construct 5,8-dihydro-isoxazolo[4,5-*c*]azepine-4-one, a novel isoxazole-annulated ring system. The scanning of literature does not reveal the synthesis of this heterocyclic system though various other ring systems including benzoxepino,¹⁶ pyridazine,¹⁷ pyrazine,¹⁸ pyrrole,¹⁹ pyrimidine,²⁰ triazole²¹ annulated to isoxazole have been reported. As was expected, the Baylis–Hillman reaction of 3-aryl-5-formylisoxazole-4-carboxylate was found to be unusually fast and the resulting product did provide the scaffold for the synthesis of 5,8-dihydroisoxazolo[4,5-*c*]azepin-4-one, a new isoxazole annulated heterocyclic system. The details of our preliminary investigations are presented here.

The Baylis–Hillman reaction of 3-aryl-5-formyl-4-isoxazolecarboxylate **1a–c** with activated alkenes without any solvent was significantly fast to afford the corresponding Baylis–Hillman adducts **2–6** along with the unidentified

polar impurities as major product. After a series of optimization studies for ascertaining the optimum reaction condition to achieve best yields of products, the anhydrous conditions using dry THF was found to be the most suitable. Though this reaction condition furnished the Baylis–Hillman adduct in excellent yields with methyl, ethyl and butyl acrylates, only moderate yield could be achieved with *tert*-butyl acrylate (Scheme 1). It will be appropriate to mention here that the presence of moisture during the Baylis–Hillman reaction of these substrates significantly reduced the yield of the products. It was envisaged that the reaction of primary amine with the acetate of the Baylis–Hillman adducts followed by subsequent intramolecular cyclization involving ester on the isoxazole nucleus and the NH groups could furnish the desired isoxazole-annulated ring system. However, this optimistic presumption was based on considerations that *Z* stereochemistry across the double bond in the generated allylic amine alone could help intramolecular ring closure reaction. Acetylation of the Baylis–Hillman adducts **2a–c**, **4a–c**, **5a,c** and **6a** with acetyl chloride and pyridine furnished the corresponding acetates **7a–c**, **8a–c**, **9a,c** and **10a** in good yields. The reaction of acetate **6a–c** with benzylamine in methanol led to completion of reaction within short periods. The TLC profile of the reaction mixture indicated the formation of two products. On the basis of spectral analysis of these products, the minor products were assigned the structure **11a–c**, while the major products were found to be **12a–c**. The stereochemistry of the product **12** was assigned as *E* by comparison with the reported data.^{12,22} This result was in accordance with the literature precedence that the nucleophilic addition of amines on the acetates of Baylis–Hillman adducts derived from acrylic esters leads to products with *E*-stereochemistry. Contrary to this observation, reactions of compounds **7a–c** with benzylamine yielded the cyclized derivatives **13a–c** and uncyclized derivative **14a–c** in almost equal quantity, while compounds **8a,c** yielded **15a,c** as the major products as compared to allylic amines **16a,c**. In the light of this observation it could be argued that *n*-butyl or *tert*-butyl ester group present in compounds **7,8** possibly facilitated the formation of *Z*-isomers of allylic amine intermediates in higher yields, which after ring closure furnished better yields of cyclized derivatives **13** and **15**. In view of these results it was considered appropriate to evaluate the formation of isoxazolo[4,5-*c*]azepin-4-one system in the Baylis–Hillman products derived from acrylonitrile since it is documented that the nucleophilic substitution in these compounds



Scheme 1 Reagents and Conditions: a. CH₂=CHEWG, DABCO, anhyd THF, r.t., 5 min; b. AcCl, pyridine, anhyd CH₂Cl₂, 0–5 °C, 5 min; c. PhCH₂NH₂, MeOH, r.t., 2–5 h.

leads to products with *Z* stereochemistry. However in a model reaction, the compound **10a** upon reaction with benzylamine afforded the cyclized derivative **17a** in minor yields only, though the stereochemistry of the allylic amine **18a** obtained as the major product was found to be *Z*. Thus it can be presumed that presence of a bulky group such as *n*-butyl or *tert*-butyl in the side chain facilitates the cyclization. Interestingly, the Baylis–Hillman adducts **5a** on reaction with benzylamine yielded only the diastereoisomeric mixture of amine **15**.

In conclusion, we have described yet another isoxazole-based fast-reacting substrate for Baylis–Hillman reaction and have accomplished the synthesis of a new isoxazole-annulated heterocycle through the Baylis–Hillman adducts derived from it. We are further exploring the details and scope of this reaction and its application towards solid-phase combinatorial synthesis.

Table 1 Compounds **3–19** Prepared

Product ^a	Yield ^b (%)	Physical Appearance	Mp (°C)	Mass (FAB ⁺ or ES ⁺) <i>m/z</i>	IR (cm ^{−1})
2a	95	yellow oil	–	318 (M ⁺ + 1)	1727 (2 ester C=O, CO ₂ Me), 3462 (OH)
2b	84	yellow oil	–	374.60 (M ⁺ + Na)	1730 (2 ester C=O, CO ₂ Me), 3429 (OH)
2c	82	yellow oil	–	386.27 (M ⁺ + 1)	1713 (ester C=O, CO ₂ Me), 1734 (ester C=O, CO ₂ Me), 3370 (OH)
3a	79	yellow oil	–	354.60 (M ⁺ + Na)	1726 (br, ester C=O, CO ₂ Et and CO ₂ Me), 3446 (OH)
4a	87	yellow oil	–	360 (M ⁺ + 1)	1739 (ester C=O, CO ₂ Bu and CO ₂ Me), 3465 (OH)
4b	83	yellow oil	–	394 (M ⁺ + 1)	1721 (ester C=O, CO ₂ Bu and CO ₂ Me), 3448 (OH)
4c	88	yellow oil	–	450.43 (M ⁺ + Na)	1732 (ester C=O, CO ₂ Bu and CO ₂ Me), 3422 (OH)
5a	57	pale yellow oil	–	381.93 (M ⁺ + Na)	1721 (ester C=O, CO ₂ <i>t</i> -Bu and CO ₂ Me), 3445 (OH)
5c	62	pale yellow solid	131–133	450.27 (M ⁺ + Na)	1722 (ester C=O, CO ₂ <i>t</i> -Bu and CO ₂ Me), 3356 (OH)
6a	79	yellow oil	–	285 (M ⁺ + 1)	1735 (ester C=O, CO ₂ Me), 2231 (C≡N), 3429 (OH)
6b	77	yellow oil	–	319 (M ⁺ + 1)	1733 (ester C=O, CO ₂ Me), 2232 (C≡N), 3423 (OH)
7a	88	pale yellow oil	–	360 (M ⁺ + 1)	1733 (br, 2 ester C=O, CO ₂ Me and COCH ₃)
7b	81	pale yellow oil	–	416.20 (M ⁺ + Na)	1733 (br, 2 ester C=O, CO ₂ Me and COCH ₃)
7c	82	pale yellow oil	–	450.20 (M ⁺ + Na)	1731 (br, 2 ester C=O, CO ₂ Me and COCH ₃)

Table 1 Compounds **3–19** Prepared (continued)

Product ^a	Yield ^b (%)	Physical Appearance	Mp (°C)	Mass (FAB+ or ES+) <i>m/z</i>	IR (cm ⁻¹)
8a	77	pale yellow oil	–	402 (M ⁺ + 1)	1731 (ester C=O, CO ₂ Bu and CO ₂ Me), 1745 (COCH ₃)
8b	77	pale yellow oil	–	458.47 (M ⁺ + Na)	1732 (ester C=O, CO ₂ Bu and CO ₂ Me), 1745 (COCH ₃)
8c	80	pale yellow oil	–	470 (M ⁺ + 1)	1732 (ester C=O, CO ₂ Me and CO ₂ Bu), 1742 (COCH ₃)
9a	92	white solid	99–101	420 (M ⁺ + 1)	1730 (br, ester C=O, CO ₂ <i>t</i> -Bu, CO ₂ Me and COCH ₃)
9c	90	colorless oil	–	471 (M ⁺ + 1)	1731 (br, ester C=O, CO ₂ <i>t</i> -Bu and CO ₂ Me), 1745 (COCH ₃)
10a	87	colorless oil	–		1731 (ester C=O, CO ₂ Me), 1745 (COCH ₃), 2217 (C≡N)
11a	9	white solid	112–113	349.80 (M ⁺ + Na)	1649 (CONH), 1725 (ester C=O, CO ₂ Me)
11b	10	white solid	154–156	410.33 (M ⁺ + 1)	1644 (amide C=O, CONH), 1721 (CO ₂ Me)
11c	7	colorless oil	–	443.20 (M ⁺ + 1)	1650 (amide C=O, CONH), 1725 (ester C=O, CO ₂ Me)
12a	63	pale yellow solid	129–131	406 (M ⁺ + 1)	1725 (2 ester C=O, CO ₂ Me), 3427 (NH)
12b	48	pale yellow oil	–	441.33 (M ⁺ + 1)	1724 (2 ester C=O, CO ₂ Me), 3410 (NH)
12c	51	pale yellow oil	–	497.27 (M ⁺ + Na)	1726 (2 ester C=O, CO ₂ Me), 3427 (NH)
13a	49	light brown oil	–	439.53 (M ⁺ + Na)	1647 (C=O), 1722 (CO ₂ Me)
13b	41	light brown oil	–	449.40 (M ⁺ + 1), 471.53 (M ⁺ + Na)	1724 (ester C=O, CO ₂ Me), 3362 (NH)
13c	43	light brown oil	–	517.00 (M ⁺ + Na)	1647 (C=O), 1722 (ester C=O, CO ₂ Me)
14a	30	light brown oil	–	471.53 (M ⁺ + Na)	1724 (ester C=O, CO ₂ Me and CO ₂ Bu), 3362 (NH)
14b	29	light brown oil	–	483.40 (M ⁺ + 1)	1726 (ester C=O, CO ₂ Me and CO ₂ Bu), 3394 (NH)
14c	27	light brown oil	–	539.23 (M ⁺ + 1)	1722 (ester C=O, CO ₂ Me and CO ₂ Bu), 3450 (NH)
15a	57	pale yellow solid	123–125	417 (M ⁺ + 1)	1647 (amide C=O, CONH), 1710 (ester C=O, CO ₂ Bu- <i>t</i>)
15c	41	white solid	138–140	485 (M ⁺ + 1)	1710 (ester C=O, CO ₂ <i>t</i> -Bu), 1654 (amide C=O, CONH)
16a	10	yellow oil	–	449 (M ⁺ + 1)	1720 (ester C=O, CO ₂ Me and CO ₂ Bu- <i>t</i>)
16c	14	yellow oil	–	517 (M ⁺ + 1)	1723 (ester C=O, CO ₂ Me and CO ₂ Bu- <i>t</i>), 3350 (NH)
17a	20	white solid	157–159	342 (M ⁺ + 1)	1641 (C=O), 2222 (C≡N)
18a	43	light brown oil	–	374.53 (M ⁺ + 1)	1726 (ester C=O, CO ₂ Me), 2193 (C≡N)
19a	67	light brown oil	–	467.23 (M ⁺ + 1)	1726 (ester C=O, CO ₂ Me), 2193 (C≡N)

^a All compounds gave satisfactory microanalyses: C ±0.4; H ±0.4; N ±0.3.^b Yields described are the one obtained after column chromatography over silica gel.

Melting points are uncorrected and were determined in capillary tubes on a hot stage apparatus containing silicon oil. IR spectra were recorded using Perkin-Elmer Spectrum RX I FTIR spectrophotometer as KBr disc or neat. ¹H NMR spectra were recorded either on a Bruker DPX-200 FT or Bruker Avance DRX-300 spectrometers, using TMS as an internal standard (chemical shifts in δ values, *J* in Hz). The ESMS were recorded through direct flow injections in Merck M-8000 LCMS system and FABMS spectra were recorded on JEOL/SX-102 spectrometer. Elemental analyses were performed on Elementar's Vario EL III microanalyzer.

Baylis–Hillman Reaction of 1a–c; General Procedure

To a stirred mixture of DABCO (60 mg, 1.8 mmol) and alkyl acrylate (4.3 mmol) was added a solution of aldehyde (4.3 mmol) in an-

hyd THF. After 5 min, 10% aq HCl was added to the reaction mixture and it was extracted with EtOAc. Usual workup of the organic layer furnished an oily residue that was passed through a small band of silica gel using a mixture of hexane–EtOAc (85:15) to yield the pure product.

Methyl 5-(1-Hydroxy-2-methoxycarbonylallyl)-3-phenylisoxazole-4-carboxylate (2a)

¹H NMR (CDCl₃, 200 MHz): δ = 3.77 (s, 3 H, CO₂CH₃), 3.79 (s, 3 H, CO₂CH₃), 4.72, 4.75 (d, 1 H, *J* = 7.2 Hz, OH), 6.07 (d, 1 H, *J* = 7.2 Hz, CH), 6.21 (s, 1 H, =CHH), 6.56 (s, 1 H, =CHH), 7.44–7.49 (m, 3 H, ArH), 7.55–7.60 (m, 2 H, ArH).

¹³C NMR (CDCl₃, 50.32 MHz): δ = 52.62 (CH₃), 53.26 (CH₃), 65.97 (CH), 127.47 (CH₂), 128.52 (CH), 129.69 (CH), 130.38 (CH),

137.25 (C), 162.62 (C), 163.52 (C), 166.00 (C), 171.65 (C), 177.67 (C), 178.67 (C).

Methyl 5-(2-Ethoxycarbonyl-1-hydroxyallyl)-3-phenylisoxazole-4-carboxylate (3a)

¹H NMR (CDCl₃, 200 MHz): δ = 1.29 (t, 3 H, *J* = 7.0 Hz, CH₃), 3.74 (s, 3 H, CO₂CH₃), 3.90 (s, 3 H, CO₂CH₃), 4.62 (br s, 1 H, OH), 6.07 (s, 1 H, CH), 6.19 (s, 1 H, =CHH), 6.56 (s, 1 H, =CHH), 7.44–7.69 (m, 5 H, ArH).

Methyl 5-(2-Butoxycarbonyl-1-hydroxyallyl)-3-phenylisoxazole-4-carboxylate (4a)

¹H NMR (CDCl₃, 200 MHz): δ = 0.92 (t, 3 H, *J* = 7.2 Hz, CH₃), 1.31–1.42 (m, 2 H, CH₂), 1.60–1.67 (m, 2 H, CH₂), 3.77 (s, 3 H, CO₂CH₃), 4.18 (t, 2 H, *J* = 6.4 Hz, CO₂CH₂), 4.65 (br, 1 H, OH), 6.07 (s, 1 H, CH), 6.19 (s, 1 H, =CHH), 6.56 (s, 1 H, =CHH), 7.43–7.48 (m, 3 H, ArH), 7.55–7.60 (m, 2 H, ArH).

Methyl 5-(2-*tert*-Butoxycarbonyl-1-hydroxyallyl)-3-phenylisoxazole-4-carboxylate (5a)

¹H NMR (CDCl₃, 200 MHz): δ = 1.46 [s, 9 H, C(CH₃)₃], 3.76 (s, 3 H, CO₂CH₃), 4.6 (br, 1 H, OH), 6.02 (s, 1 H, CH), 6.10 (d, 1 H, *J* = 0.8 Hz, =CHH), 6.47 (d, 1 H, *J* = 0.8 Hz, =CHH), 7.44–7.47 (m, 3 H, ArH), 7.55–7.57 (m, 2 H, ArH).

Methyl 5-(2-Cyano-1-hydroxyallyl)-3-phenylisoxazole-4-carboxylate (6a)

¹H NMR (CDCl₃, 200 MHz): δ = 3.78 (s, 3 H, CO₂CH₃), 4.97 (br s, 1 H, OH), 5.80 (d, 1 H, *J* = 1.4 Hz, CH), 6.24 (s, 1 H, *J* = 1.4 Hz, =CHH), 6.31 (d, 1 H, *J* = 1.4 Hz, =CHH), 7.45–7.59 (m, 5 H, ArH).

Methyl 3-(4-Chlorophenyl)-5-(2-cyano-1-hydroxyallyl)isoxazole-4-carboxylate (6b)

¹H NMR (CDCl₃, 200 MHz): δ = 3.80 (s, 3 H, CO₂CH₃), 4.97 (br s, 1 H, OH), 5.79 (s, 1 H, CH), 6.24 (d, 1 H, *J* = 1.2 Hz, =CHH), 6.32 (s, 1 H, *J* = 1.2 Hz, =CHH), 7.37–7.62 (m, 4 H, ArH).

Acetylation of 2–6; General Procedure

To a stirred solution of appropriate compound from 2–6 (3.25 mmol) in anhyd CH₂Cl₂ (5 mL) was added pyridine (0.39 mL, 4.9 mmol) followed by a dropwise addition of solution of acetyl chloride (0.46 mL, 6.5 mmol) in anhyd CH₂Cl₂ (3 mL) at 0 °C. After the addition was complete, the reaction was continued at 0 °C for 5 min. The reaction mixture was extracted with CH₂Cl₂ (2 × 15 mL) and H₂O (30 mL). The organic layers were combined, washed with brine, dried (Na₂SO₄) and evaporated to obtain an oily residue. The residue was purified on a small band of silica gel using hexane–EtOAc (85:15) as eluent to obtain pure acetates.

Methyl 5-(1-Acetoxy-2-methoxycarbonylallyl)-3-phenylisoxazole-4-carboxylate (7a)

¹H NMR (CDCl₃, 300 MHz): δ = 2.21 (s, 3 H, COCH₃), 3.82 (s, 3 H, CO₂CH₃), 3.83 (s, 3 H, CO₂CH₃), 6.05 (s, 1 H, =CHH), 6.62 (s, 1 H, =CHH), 7.32 (s, 1 H, CH), 7.47–7.51 (m, 3 H, ArH), 7.66–7.69 (m, 2 H, ArH).

Methyl 5-(1-Acetoxy-2-butoxycarbonylallyl)-3-phenylisoxazole-4-carboxylate (8a)

¹H NMR (CDCl₃, 200 MHz): δ = 0.85 (t, 3 H, *J* = 7.2 Hz, CH₃), 1.18–1.35 (m, 2 H, CH₂), 1.48–1.60 (m, 2 H, CH₂), 2.12 (s, 3 H, COCH₃), 3.67 (s, 3 H, CO₂CH₃), 4.11 (t, 2 H, *J* = 6.4 Hz, CO₂CH₂), 5.91 (s, 1 H, =CHH), 6.53 (s, 1 H, =CHH), 7.23 (s, 1 H, CH), 7.29–7.30 (m, 3 H, ArH), 7.44 (s, 2 H, ArH).

Methyl 5-(1-Acetoxy-2-*tert*-butoxycarbonylallyl)-3-phenylisoxazole-4-carboxylate (9a)

¹H NMR (CDCl₃, 200 MHz): δ = 1.45 [s, 9 H, C(CH₃)₃], 2.18 (s, 3 H, COCH₃), 3.79 (s, 3 H, CO₂CH₃), 5.88 (d, 1 H, *J* = 1.2 Hz, CH), 6.51 (s, 1 H, =CHH), 7.21 (s, 1 H, =CHH), 7.44–7.48 (m, 3 H, ArH), 7.63–7.67 (m, 2 H, ArH).

Methyl 5-(1-Acetoxy-2-cyanoallyl)-3-phenylisoxazole-4-carboxylate (10a)

¹H NMR (CDCl₃, 200 MHz): δ = 2.23 (s, 3 H, COCH₃), 3.81 (s, 3 H, CO₂CH₃), 6.26 (s, 1 H, =CHH), 6.28 (s, 1 H, =CHH), 7.03 (s, 1 H, CH), 7.45–7.52 (m, 3 H, ArH), 7.56–7.65 (s, 2 H, ArH).

Reaction of 7–10 with Benzylamine; General Procedure

To the appropriate solution of acetate (1.2 mmol) in MeOH was added benzylamine (0.27 mL, 2.5 mmol) under stirring at r.t. The reaction was allowed to proceed for 2–5 h. The excess solvent was evaporated and the residue was subjected to column chromatography over silica gel using hexane–EtOAc (75:25) mixture to yield the products as solid or oil.

Methyl 5-Benzyl-4-oxo-3-phenyl-5,6-dihydro-4*H*-isoxazolo[4,5-*c*]azepine-7-carboxylate (11a)

¹H NMR (CDCl₃, 200 MHz): δ = 3.76 (s, 3 H, CO₂CH₃), 4.20 (s, 2 H, CH₂), 4.72 (s, 2 H, CH₂), 7.46–7.53 (m, 5 H, ArH), 7.61–7.65 (m, 2 H, ArH), 7.69 (s, 1 H, =CH), 7.84–7.89 (m, 2 H, ArH).

Methyl 5-(3-Benzylamino-2-methoxycarbonylpropenyl)-3-phenylisoxazole-4-carboxylate (12a)

¹H NMR (CDCl₃, 200 MHz): δ = 3.74 (s, 2 H, CH₂), 3.76 (s, 3 H, CO₂CH₃), 3.78 (s, 3 H, CO₂CH₃), 3.95 (s, 2 H, CH₂), 7.21–7.26 (m, 5 H, ArH), 7.44–7.49 (m, 3 H, ArH), 7.58–7.61 (m, 2 H, ArH), 7.85 (s, 1 H, =CH).

Butyl 5-Benzyl-4-oxo-3-phenyl-5,6-dihydro-4*H*-isoxazolo[4,5-*c*]azepine-7-carboxylate (13a)

¹H NMR (CDCl₃, 200 MHz): δ = 0.93 (t, 3 H, *J* = 7.2 Hz, CH₃), 1.25–1.42 (m, 2 H, CH₂), 1.58–1.71 (m, 2 H, CH₂), 3.98 (s, 2 H, CH₂), 4.20 (t, 2 H, *J* = 6.4 Hz, CO₂CH₂), 4.72 (s, 2 H, CH₂), 7.23 (s, 1 H, =CH), 7.29–7.30 (m, 3 H, ArH), 7.44 (s, 2 H, ArH).

Methyl 5-(3-Benzylamino-2-butoxycarbonylpropenyl)-3-phenylisoxazole-4-carboxylate (14a)

¹H NMR (CDCl₃, 200 MHz): δ = 0.90 (t, 3 H, *J* = 7.2 Hz, CH₃), 1.25–1.39 (m, 2 H, CH₂), 1.40–1.60 (m, 2 H, CH₂), 3.70 (s, 2 H, CH₂), 3.77 (s, 3 H, CO₂CH₃), 3.87 (s, 2 H, CH₂), 4.27 (t, 2 H, *J* = 6.4 Hz, CO₂CH₂), 7.19–7.69 (m, 11 H, ArH and =CH).

***tert*-Butyl 5-Benzyl-4-oxo-3-phenyl-5,6-dihydro-4*H*-isoxazolo[4,5-*c*]azepine-7-carboxylate (15a)**

¹H NMR (CDCl₃, 200 MHz): δ = 1.50 [s, 9 H, C(CH₃)₃], 4.21 (s, 2 H, CH₂), 4.74 (s, 2 H, CH₂), 7.28–7.35 (m, 5 H, ArH), 7.45–7.52 (m, 3 H, ArH), 7.63 (s, 1 H, =CH), 7.85–7.89 (m, 2 H, ArH).

¹³C NMR (CDCl₃, 50.32 MHz): δ = 27.92 [C(CH₃)₃], 44.47 (CH₂), 51.12 (CH₂), 82.87 (CH), 125.05 (CH), 127.75 (CH), 128.29 (CH), 128.42 (CH), 128.69 (CH), 129.11 (CH), 130.30 (CH), 137.30 (C), 138.66 (C), 162.66 (C), 163.52 (C), 166.00 (C), 171.65 (C).

Methyl 5-(3-Benzylamino-2-*tert*-butoxycarbonylpropenyl)-3-phenylisoxazole-4-carboxylate (16a)

¹H NMR (CDCl₃, 200 MHz): δ = 1.54 [s, 9 H, C(CH₃)₃], 3.73 (s, 2 H, CH₂), 3.74 (s, 3 H, CO₂CH₃), 4.02 (s, 2 H, CH₂), 7.15–7.19 (m, 5 H, ArH), 7.40–7.50 (m, 3 H, ArH), 7.57–7.62 (m, 2 H, ArH), 7.76 (s, 1 H, =CH).

5-Benzyl-4-oxo-3-phenyl-5,6-dihydro-4H-isoxazolo[4,5-c]azepine-7-carbonitrile (17a)

¹H NMR (CDCl₃, 300 MHz): δ = 4.09 (s, 2 H, CH₂), 4.76 (s, 2 H, CH₂), 7.27–7.50 (s, 9 H, ArH and =CH), 7.50–7.53 (m, 2 H, ArH).

Methyl 5-(3-Benzylamino-2-cyanopropenyl)-3-phenylisoxazole-4-carboxylate (18a)

¹H NMR (CDCl₃, 300 MHz): δ = 3.63 (s, 2 H, CH₂), 3.76 (s, 3 H, CO₂CH₃), 3.86 (s, 2 H, CH₂), 7.20–7.63 (s, 11 H, ArH and =CH).

Methyl 5-(3-Benzylamino-2-tert-butoxycarbonyl-1-hydroxypropyl)-3-phenylisoxazole-4-carboxylate (19a) (Diastereomeric Mixture)

¹H NMR (CDCl₃, 200 MHz): δ = 1.46, 1.48 [2 s, 18 H, 2 C(CH₃)₃], 3.03–3.06 (m, 1 H, CH), 3.33–3.37 (m, 1 H, CH), 3.76, 3.81 (2 s, 4 H, CH₂), 3.86 (s, 6 H, 2 CO₂CH₃), 3.92, 3.96 (2 s, 4 H, CH₂), 5.73, 5.74 (d, 1 H, 2.6 Hz, CH), 5.93, 5.94 (d, 1 H, 2.6 Hz, CH), 7.28–7.37 (m, 10 H, ArH), 7.46–7.49 (m, 6 H, ArH), 7.65–7.67 (m, 6 H, ArH).

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