Baylis-Hillman reaction assisted synthesis of substituted 5,8-dihydro-isoxazolo[4,5-c]azepin-4-one: A novel isoxazole-annulated heterocycle§

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

Key words: , Baylis-Hillman reaction, acetate, 3-aryl-5-formyl-isoxazole-4-carboxylate, 5,8-dihydro-isoxazole(4,5-c)azepine-4-one.

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.[1,2] These compounds have been obtained either directly as products of Baylis-Hillman reaction or by appropriate modification of derivatives of the Baylis-Hillman adducts.[1-10]

Our research efforts are concerned with the exploration of the Baylis-Hillman reaction of substituted isoxazole-carbaldehydes and the synthetic utility of the resulting products.[11-13] In this context we have recently reported the synthesis of 5-formyl-3-aryl-isoxazole-4-carboxylate.[14] 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-isoxazole(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,[15] pyridazine,[16] pyrazine,[17] pyrrole,[18] pyrimidine,[19] triazole[20] annulated to isoxazole have been reported. As was expected, the Baylis-Hillman reaction of 3-aryl-5-formyl-isoxazole-4-carboxylate was found to be unusually fast and the resulting product did provide the scaffold for the synthesis of 5,8-dihydro-isoxazolo[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 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 corresponding acetates **7-8a-c, 9a,c** and **10a** in good yields. The reaction of acetate **6a-c** with benzyl amine 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.[11,21] 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 benzyl amine 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 compound **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 leads to products with Z-stereochemistry. However in a model reaction, the compound **10a** upon reaction with benzyl amine 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 benzyl

amine 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.

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's Spectrum RX I FTIR spectrophotometer as KBr disc or neat. ^{1}H 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 *J*EOL/ SX-102 spectrometer. Elemental analyses were performed on Elementar's Vario EL *III* microanalyzer.

General procedure for the Baylis-Hillman reaction:

To the prestirred mixture of DABCO (60 mg, 1.8 mmol) and alkyl acrylate (4.3 mmol) was added a solution of aldehyde (4.3 mmol) in dry THF. After 2 min. 10 % aqueous HCl was added to the reaction mixture and it was extracted with ethyl acetate. Usual work up of the organic layer furnished an oily residue that was passed through a small band of silica gel using a mixture of hexane: ethylacetate (85: 15, v/v) to yield the pure product.

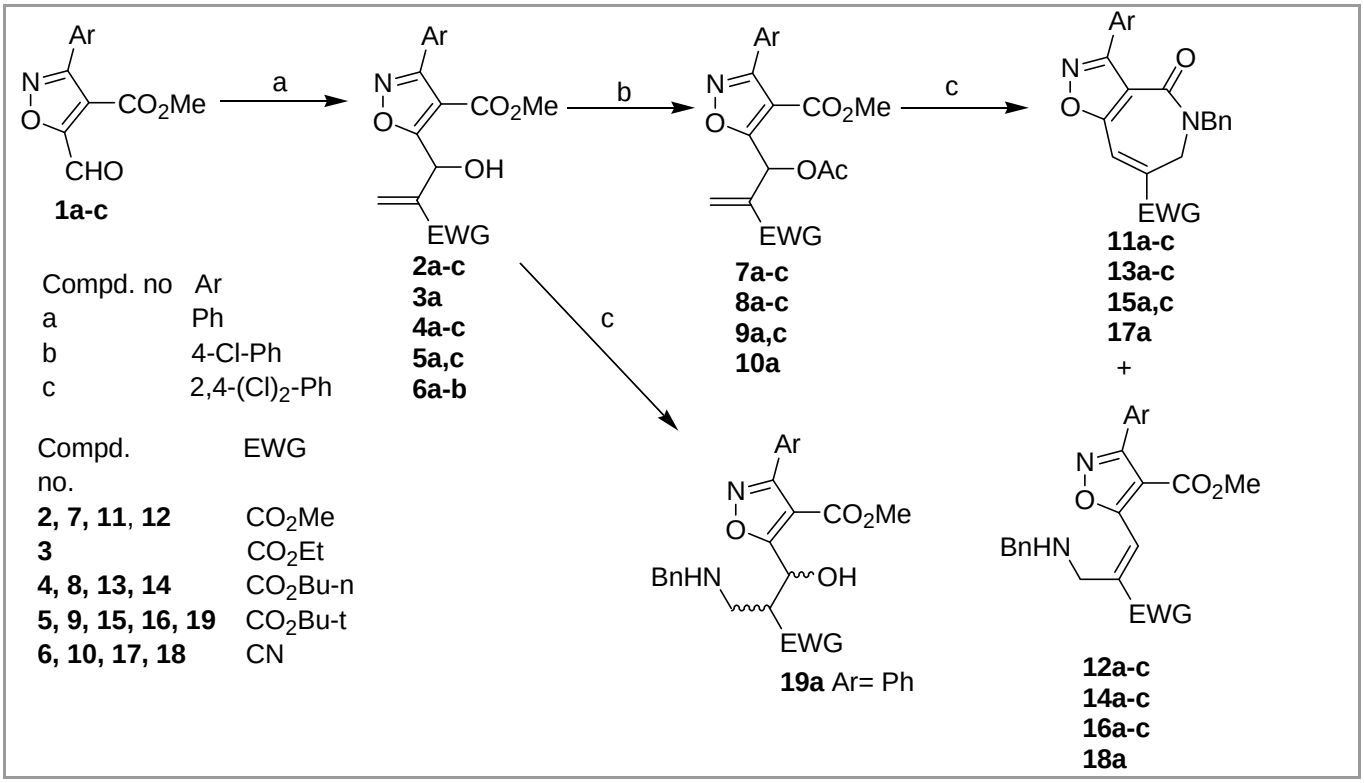
5-(1-Hydroxy-2-methoxycarbonyl-allyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (2a)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 3.77 (s, 3H, CO_2CH_3), 3.79 (s, 3H, CO_2CH_3), 4.72, 4.75 (d, 1H, *J*= 7.2 Hz, OH), 6.06, 6.09 (d, 1H, *J*= 7.2 Hz, CH), 6.21 (s, 1H, =CH*H*), 6.56 (s, 1H, =C*H*H), 7.44-7.49 (m, 3H, ArH), 7.55-7.60 (m, 2H, ArH).

^{13}C NMR ($CDCl_3$, 50.32 MHz) δ= 52.62 (CH_3), 53.26 (CH_3), 65.97 (CH), 127.47 (CH_2), 128.52 (CH), 129.69 (CH)130.38 (CH), 137.25 (C), 162.62 (C), 163.52 (C), 166.00 (C), 171.65 (C), !77.67 (C), 178.67 (C).

5-(2-Ethoxycarbonyl-1-hydroxy-allyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (3a)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 1.29 (t, 3H, J= 7.0 Hz, CH_3), 3.74 (s, 3H, CO_2CH_3), 3.90 (s, 3H, CO_2CH_3), 4.62 (brs, 1H, OH), 6.07 (s, 1H, CH), 6.19 (s, 1H, =CH*H*), 6.56 (s, 1H, =C*H*H), 7.44-7.69 (m, 5H, ArH).



Scheme 1 *Reagents and Conditions*: a. CH_2=CHEWG, DABCO, dry THF, rt, 5min.; b. AcCl, Pyridine, dry CH_2Cl_2, 0-5°C, 2min.; $PhCH_2NH_2$, CH3OH, rt, 2-5h.

Table 1 Characterization data for compounds[a] the synthesized compounds.

Compound No	Yield[b] (%)	Physical Appearance	Mp (°C)	Mass (*m/z*) (FAB+ or ES+)	υ_{max} (cm^{-1})
2a	95	Yellow oil	-	318 (M^++1)	1727 (2 X CO_2Me), 3462 (OH)
2b	84	Yellow oil	-	374.60 (M^++Na)	1730 (2 X CO_2Me), 3429 (OH)
2c	82	Yellow oil	-	386.27 (M^++1)	1713 (CO_2Me), 1734 (CO_2Me), 3370 (OH)
3a	79	Yellow oil	-	354.60 (M^++Na)	1726 (br) (CO_2Et and CO_2Me), 3446 (OH)
4a	87	Yellow oil	-	360 (M^++1)	1739 (CO_2n-Bu and CO_2Me), 3465 (OH)
4b	83	Yellow oil	-	394 (M^++1)	1721 (CO_2n-Bu and CO_2Me), 3448 (OH)
4c	88	Yellow oil	-	450.43 (M^++Na)	1732 (CO_2n-Bu and CO_2Me), 3422 (OH)
5a	57	Pale yellow oil	-	381.93 (M^++Na)	1721 (CO_2t-Bu and CO_2Me), 3445 (OH)
5c	62	Pale yellow solid	131-133	450.27 (M^++Na)	1722 (CO_2t-Bu and CO_2Me), 3356 (OH)
6a	79	Yellow oil	-	285 (M^++1)	1735 (CO_2Me), 2231 (CN), 3429 (OH)
6b	77	Yellow oil	-	319 (M^++1)	1733 (CO_2Me), 2232 (CN), 3423 (OH)
7a	88	Pale yellow oil	-	360 (M^++1)	1733 (br) (2 X CO_2Me and $COCH_3$)
7b	81	Pale yellow oil	-	416.20 (M^++Na)	1733 (br) (2 X CO_2Me and $COCH_3$)
7c	82	Pale yellow oil	-	450.20 (M^++Na)	1731 (br) (2 X CO_2Me and $COCH_3$)
8a	77	Pale yellow oil	-	402 (M^++1)	1731 (CO_2*n*-Bu and CO_2Me), 1745 ($COCH_3$)
8b	77	Pale yellow oil	-	458.47 (M^++Na)	1732 (CO_2*n*-Bu and CO_2Me), 1745 ($COCH_3$)
8c	80	Pale yellow oil	-	470 (M^++1)	1732 (CO_2Me and CO_2-*n*-Bu), 1742 ($COCH_3$)
9a	92	White solid	99-101	420 (M^++1)	1730 (br) (CO_2-*t*-Bu, CO_2Me and $COCH_3$)
9c	90	Colorless oil	-	471 (M^++1)	1731 (br)(CO_2-*t*-Bu and CO_2Me) , 1745 ($COCH_3$)
10a	87	Colorless oil	-		1731 (CO_2Me), 1745 ($COCH_3$), 2217 (CN)
11a	9	White solid	112-113	349.80 (M^++Na)	1649 (CONH), 1725 (CO_2Me)
11b	10	White solid	154-156	410.33 (M^++1)	1644 (CONH), 1721 (CO_2Me)
11c	7	Colorless oil	-	443.20 (M^++1)	1650 (CONH), 1725 (CO_2Me)
12a	63	Pale yellow solid	129-131	406 (M^++1)	1725 (2 X CO_2-Me), 3427 (NH)
12b	48	Pale yellow oil	-	441.33 (M^++1)	1724 (2 X CO_2-Me), 3410 (NH)
12c	51	Pale yellow oil	-	497.27 (M^++Na)	1726 (2 X CO_2-Me), 3427 (NH)
13a	49	Light brown oil	-	439.53 (M^++Na)	1647 (CO) ,1722 (CO_2Me)
13b	41	Light brown oil	-	449.40 (M^++1), 471.53 (M^++Na)	1724 (CO_2Me), 3362 (NH)
13c	43	Light brown oil	-	517.00 (M^++Na)	1647 (CO), 1722 (CO_2Me)
14a	30	Light brown oil	-	471.53 (M^++Na)	1724 (CO_2Me and CO_2-*n*-Bu), 3362 (NH)
14b	29	Light brown oil	-	483.40 (M^++1)	1726 (CO_2Me and CO_2-*n*-Bu), 3394 (NH)
14c	27	Light brown oil	-	539.23 (M^++1)	1722 (CO_2Me and CO_2-*n*-Bu), 3450 (NH)
15a	57	Pale yellow solid	123-125	417 (M^++1)	1647 (CONH), 1710 (CO_2-t-Bu)
15c	41	White solid	138-140	485 (M^++1)	1710 (CO_2-t-Bu), 1654 (CONH)
16a	10	Yellow oil	-	449 (M^++1)	1720 (CO_2Me and CO_2-*t*-Bu)
16c	14	Yellow oil	-	517 (M^++1)	1723 (CO_2Me and CO_2-t-Bu), 3350 (NH)
17a	20	White solid	157-159	342 (M^++1)	1641 (CO), 2222 (CN)
18a	43	Light brown oil	-	374.53 (M^++1)	1726 (CO_2Me), 2193 (CN)
19a	67	Light brown oil	-	467.23 (M^++1)	1726 (CO_2Me), 2193 (CN)

[a] All compounds gave satisfactory microanalyses. [b] Yields described are the one obtained after column chromatography over silica gel.

5-(2-Butoxycarbonyl-1-hydroxy-allyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (4a)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 0.92 (t, 3H, *J*= 7.2 Hz, CH_3), 1.31-1.42 (m, 2H, CH_2), 1.60-1.67 (m, 2H, CH_2), 3.77 (s, 3H, CO_2CH_3), 4.18 (t, 2H, *J*= 6.4 Hz, CO_2CH_2), 4.65 (br, 1H, OH), 6.07 (s, 1H, CH), 6.19 (s, 1H, =CH*H*), 6.56 (s, 1H, =C*H*H), 7.43-7.48 (m, 3H, ArH), 7.55-7.60 (m, 2H, ArH)

5-(2-tert-Butoxycarbonyl-1-hydroxy-allyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (5a)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 1.46 (s, 9H, $C(CH_3)_3$), 3.76 (s, 3H, CO_2CH_3), 4.6 (br, 1H, OH), 6.02 (s, 1H, CH), 6.104, 6.108 (d, 1H, *J*= 0.8 Hz, =CH*H*), 6.466, 6.470 (d, 1H, *J*= 0.8 Hz, =C*H*H), 7.44-7.47 (m, 3H, ArH), 7.55-7.57 (m, 2H, ArH)

5-(2-Cyano-1-hydroxy-allyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (6a)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 3.78 (s, 3H, CO_2CH_3), 4.97 (brs, 1H, OH), 5.798, 5.805 (d, 1H, *J*= 1.4 Hz, CH), 6.234, 6.241 (s, 1H, *J*= 1.4 Hz, =CH*H*), 6.305, 6.313 (s, 1H, *J*= 1.4 Hz, =C*H*H), 7.45-7.59 (m, 5H, ArH).

3-(4-Chloro-phenyl)-5-(2-cyano-1-hydroxy-allyl)-isoxazole-4-carboxylic acid methyl ester (6b)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 3.80 (s, 3H, CO_2CH_3), 4.97 (brs, 1H, OH), 5.79 (s, 1H, CH), 6.241, 6.246 (s, 1H, *J*= 1.2 Hz, =CH*H*), 6.313, 6.319 (s, 1H, *J*= 1.2 Hz, =C*H*H), 7.37-7.62 (m, 4H, ArH).

General procedure for Acetylation:

To a stirred solution of appropriate compound from 2, 4-5 (3.25 mmol) in dry dichloromethane (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 dry dichloromethane (3 mL) at 0 ^{o}C. After the addition was complete, the reaction was continued at 0 ^{o}C for 5min. The reaction mixture was extracted with dichloromethane (2 X 15 mL) and water (30mL). The organic layers were combined, washed with brine, dried over anhyd. Na_2SO_4 and evaporated to obtain an oily residue. The residue was purified on a small band of silica gel using hexane: ethyl acetate (85: 15, v/v) as eluent to obtain pure acetates.

5-(1-Acetoxy-2-methoxycarbonyl-allyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (7a)

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 2.21 (s, 3H, $COCH_3$), 3.82 (s, 3H, CO_2CH_3), 3.83 (s, 3H, CO_2CH_3), 6.05 (s, 1H, =CH*H*), 6.62 (s, 1H, =C*H*H), 7.32 (s, 1H, CH), 7.47-7.51 (m, 3H, ArH), 7.66-7.69 (m, 2H, ArH).

5-(1-Acetoxy-2-butoxycarbonyl-allyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (8a)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 0.85 (t, 3H, *J*= 7.2 Hz, CH_3), 1.18-1.35 (m, 2H, CH_2), 1.48-1.60 (m, 2H, CH_2), 2.12 (s, 3H, $COCH_3$), 3.67 (s, 3H, CO_2CH_3), 4.11 (t, 2H, *J*= 6.4 Hz, CO_2CH_2), 5.91 (s, 1H, =CH*H*), 6.53 (s, 1H, =C*H*H), 7.23 (s, 1H, CH), 7.29-7.30 (m, 3H, ArH), 7.44 (s, 2H, ArH).

5-(1-Acetoxy-2-tert-butoxycarbonyl-allyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (9a)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 1.45 (s, 9H, $C(CH_3)_3$), 2.18 (s, 3H, $COCH_3$), 3.79 (s, 3H, CO_2CH_3), 5.879, 5.885 (d, 1H, *J*= 1.2 Hz, CH), 6.51 (s, 1H, =CH*H*), 7.21 (s, 1H, =C*H*H), 7.44-7.48 (m, 3H, ArH), 7.63-7.67 (m, 2H, ArH).

5-(1-Acetoxy-2-cyano-allyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (10a)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 2.23 (s, 3H, $COCH_3$), 3.81 (s, 3H, CO_2CH_3), 6.26 (s, 1H, =CH*H*), 6.28 (s, 1H, =C*H*H), 7.03 (s, 1H, CH), 7.45-52 (m, 3H, ArH), 7.56-7.65 (s, 2H, ArH).

General Procedure for reaction with benzyl amine:

To the appropriate solution of acetate (1.2 mmol) in methanol was added benzyl amine (0.27mL, 2.5 mmol) under stirring at rt. 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-ethyl acetate (75:25, v/v) mixture to yield the products as solid or oil.

5-Benzyl-4-oxo-3-phenyl-5,6-dihydro-4H-isoxazolo-[4,5-c]azepine-7-carboxylic acid methyl ester (11a)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 3.76 (s, 3H, CO_2CH_3), 4.20 (s, 2H, CH_2), 4.72 (s, 2H, CH_2), 7.46-7.53 (m, 5H, ArH), 7.61-7.65 (m, 2H, ArH), 7.69 (s, 1H, =CH), 7.84-7.89 (m, 2H, ArH).

5-(3-Benzylamino-2-methoxycarbonyl-propenyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (12a)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 3.74 (s, 2H, CH_2), 3.76 (s, 3H, CO_2CH_3), 3.78 (s, 3H, CO_2CH_3), 3.95 (s, 2H, CH_2), 7.21-7.26 (m, 5H, ArH), 7.44-7.49 (m, 3H, ArH), 7.58-7.61 (m, 2H, ArH), 7.85 (s, 1H, =CH).

5-Benzyl-4-oxo-3-phenyl-5,6-dihydro-4H-isoxazolo[4,5-c]azepine-7-carboxylic acid butyl ester (13a)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 0.93 (t, 3H, *J*= 7.2 Hz, CH_3), 1.25-1.42 (m, 2H, CH_2), 1.58-1.71 (m, 2H, CH_2), 3.98 (s, 2H, CH_2), 4.20 (t, 2H, *J*= 6.4 Hz, CO_2CH_2), 4.72 (s, 2H, CH_2), 7.23 (s, 1H, =CH), 7.29-7.30 (m, 3H, ArH), 7.44 (s, 2H, ArH).

5-(3-Benzylamino-2-butoxycarbonyl-propenyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (14a)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 0.90 (t, 3H, *J*= 7.2 Hz, CH_3), 1.25-1.39 (m, 2H, CH_2), 1.40-1.60 (m, 2H, CH_2), 3.70 (s, 2H, CH_2), 3.77 (s, 3H, CO_2CH_3), 3.87 (s, 2H, CH_2), 4.27 (t, 2H, *J*= 6.4 Hz, CO_2CH_2), 7.19-7.69 (m, 11H, ArH and =CH)

5-Benzyl-4-oxo-3-phenyl-5,6-dihydro-4H-isoxazolo[4,5-c]azepine-7-carboxylic acid *tert*-butyl ester (15a)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 1.50 (s, 9H, $C(CH_3)_3$), 4.21 (s, 2H, CH_2), 4.74 (s, 2H, CH_2), 7.28-7.35 (m, 5H, ArH), 7.45-7.52 (m, 3H, ArH), 7.63 (s, 1H, =CH), 7.85-7.89 (m, 2H, ArH)

^{13}C NMR ($CDCl_3$, 50.32 MHz) δ= 27.92 ($C(CH_3)_3$), 44.47 (CH_2), 51.12 (CH_2), 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).

5-(3-Benzylamino-2-tert-butoxycarbonyl-propenyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (16a)

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.54 (s, 9H, $C(CH_3)_3$), 3.73 (s, 2H, CH_2), 3.74 (s, 3H, CO_2CH_3), 4.02 (s, 2H, CH_2), 7.15-7.19 (m, 5H, ArH), 7.40-7.50 (m, 3H, ArH), 7.57-7.62 (m, 2H, ArH), 7.76 (s, 1H, =CH)

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

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 4.09 (s, 2H, CH_2), 4.76 (s, 2H, CH_2), 7.27-7.50 (s, 9H, ArH and =CH), 7.50-7.53 (m, 2H, ArH)

5-(3-Benzylamino-2-cyano-propenyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (18a)

^{1}H NMR ($CDCl_3$, 300 MHz) δ= 3.63 (s, 2H, CH_2), 3.76 (s, 3H, CO_2CH_3), 3.86 (s, 2H, CH_2), 7.20-7.63 (s, 11H, ArH and =CH).

5-(3-Benzylamino-2-tert-butoxycarbonyl-1-hydroxy-propyl)-3-phenyl-isoxazole-4-carboxylic acid methyl ester (19a) (diastereomeric mixture)

^{1}H NMR ($CDCl_3$, 200 MHz) δ= 1.46, 1.48 (2s, 18H, 2 X $C(CH_3)_3$, 3.03-3.06 (m, 1H, CH), 3.33-3.37 (m, 1H, CH), 3.76, 3.81 (2s, 4H, CH_2), 3.86 (s, 6H, 2 X CO_2CH_3), 3.92, 3.96 (2s, 4H, CH_2), 5.73, 5.74 (d, 1H, 2.6 Hz, CH), 5.93, 5.94 (d, 1H, 2.6 Hz, CH), 7.28-7.37 (m, 10H, Ar-H), 7.46-7.49 (m, 6H, Ar-H), 7.65-7.67 (m, 6H, Ar-H).

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