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Tetrahedron
Tetrahedron 64 (2008) 2979–2991
www.elsevier.com/locate/tet

Synthesis of substituted 3-methylene-2-pyridones from Baylis–Hillman derivatives and its application for the generation of 2-pyridone substituted spiroisoxazolines ☆

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Received 12 October 2007; received in revised form 1 January 2008; accepted 17 January 2008
Available online 25 January 2008

Abstract

The synthesis of substituted 3-methylene-2-pyridones via S_N2 displacement reaction of nucleophiles bearing a keto group on the acetyl derivative of Baylis–Hillman adducts of acrylonitrile followed by TFA/H_2SO_4-mediated intramolecular cyclization is described. The utility of these pyridone derivatives for the synthesis of new spiroisoxazolines in highly regio- and stereo-selective fashion is also illustrated. The structure of the spiroisoxazolines has been secured via X-ray crystallographic analysis.

Keywords: Baylis–Hillman; 2-Pyridone; S_N2 reaction; Spiroisoxazoline

1. Introduction

The 2-pyridone core structure is an attractive target for synthetic organic chemists[1] owing to its significance in current medicinal chemistry.[2] In addition, 2-pyridone constitutes a substructural component of several naturally occurring compounds such as nothapodytine-B, akanthomycin, and sempervilam. Moreover, 2-pyridone derivatives serve as viable synthons to pyridine, piperidine, quinolizidine, and indolizidine alkaloids[3] and pyridone-tethered systems for dyes and pigments.[4]

In recent years products of the Baylis–Hillman reaction and the derivatives produced from them have been effectively utilized for the generation of diverse molecular skeletons employing simple alterations.[5] Especially, products of a variety of nucleophilic displacement reactions either in S_N2 or S_N2' fashion with the acetates or the allyl bromides afforded by the Baylis–Hillman adducts enable the construction of a variety of heterocyclic motifs.[6] In particular, scaffolds containing exocyclic C–C double bond could be readily synthesized from them. Such compounds in turn are excellent substrates for spirocyclic heterocycles. In this context, we have recently demonstrated practical syntheses of α-methylene-δ-valerolactones,[6b] 3-methylene-gluteramides,[6c] 3-methylene-2-pyrrolidinones,[6e] and 3-methylene-[1,5]-benzodiazepin-2-ones.[6f] In continuation of our program aimed at construction of heterocyclic scaffolds from derivatives of the Baylis–Hillman reaction, we reasoned that the S_N2 displacement reaction of the Baylis–Hillman acetate of acrylonitrile with a nucleophile containing a carbonyl moiety would provide a product which upon acid hydrolysis of the nitrile group followed by intramolecular cyclization should result in a highly substituted 2-pyridone bearing an exocyclic double bond at 3-position. Our reasoning was influenced by an elegant report by Murahashi et al. wherein they described the transformation of δ-ketonitriles to 2-pyridones in the presence of ruthenium catalyst in water.[7] Moreover the enolization of the keto group under basic condition in the derivatives of the Baylis–Hillman adduct is also precedent in the literature.[8]

Herein, we now describe a facile synthesis of highly substituted 3-methylene-2-pyridone derivatives. In order to

☆ CDRI Communication no. 7325.

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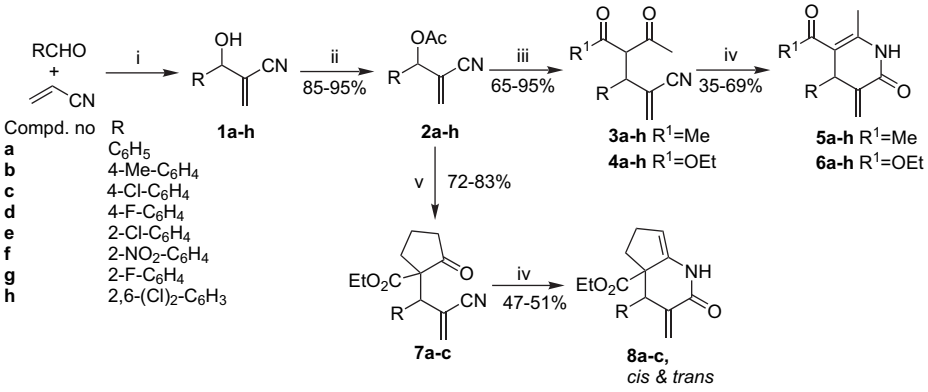
doi:10.1016/j.tet.2008.01.074



Scheme 1. Reagents and conditions: (i) DABCO, neat, rt, 0.5–15 h; (ii) AcCl, pyridine, CH_2Cl_2, 0 °C to rt, 3 h; (iii) DABCO, acetyl acetone or ethylacetoacetate, THF/H_2O (1:1, v/v), rt, 2 h; (iv) TFA/H_2SO_4 (4:1, v/v), rt, 5 min for **5** and **6** and 7 min for 8; (v) DABCO, ethylcyclopentanone-2-carboxylate, THF/H_2O (1:1, v/v), rt, 2 h.

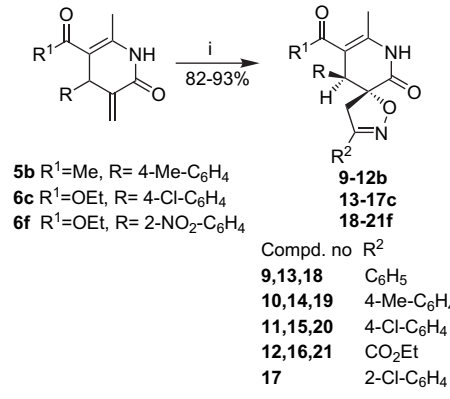
illustrate the utility of these pyridones, we have employed them as dipolarophiles in 1,3-dipolar cycloaddition reactions with nitrile oxides to obtain spiroheterocyclic system containing 2-pyridone and isoxazoline rings.

2. Results and discussion

Initially the Baylis–Hillman adducts **1a–h** obtained by the reaction of several benzaldehydes with acrylonitrile were acetylated with acetyl chloride in the presence of pyridine in dichloromethane to yield acetates **2a–h** in excellent yields. The substitution reaction between **2a–f** and acetyl acetone or ethylacetoacetate in the presence of DABCO in a THF/H_2O mixture yielded the respective products **3–4a–h** (Scheme 1). Moorthy and Singhal have recently described a highly selective conversion of nitrile to amides.[9] Adopting a similar protocol, compound **3a** was treated with a 4:1 mixture of TFA/H_2SO_4 at room temperature. It was pleasing to observe that the reaction was completed in <5 min to afford compound **5a**. In parallel we investigated the reaction of **3a** with neat H_2SO_4, H_2SO_4 in methanol, and neat TFA since these systems have been often employed for the hydrolysis of nitriles to amides. The neat H_2SO_4 too was able to transform **3a** to **5a** within 10 min but the yield of isolated **5a** was limited to 28% during optimization. On the other hand the reaction did not go to completion even after 24 h when H_2SO_4 in methanol was used while TFA alone was ineffective for this transformation. Notably, a better yield of 2-pyridone derivative was achieved when the column chromatography was accomplished on deactivated silica gel. The generality of the strategy was evaluated by subjecting several substrates **3b–h** and **4a–h** to the same reaction conditions to yield **5b–h** and **6a–h**, respectively. However, during the cyclization of **3h** to **5h**, formation of a side product was observed, which accounted for the low yields of product for this particular substrate.

With a view to expanding the scope of this strategy for the generation of annulated 3-methylene-2-pyridones, compounds **2a–c** were treated with cyclopentanone-2-carboxylate in the presence of DABCO to furnish products **7a–c** in good yields. Similar treatment of **7a–c** with a mixture of TFA/H_2SO_4 (4:1, v/v) yielded the products **8a–c** in moderate yields as diastereoisomeric mixture. Careful silica gel column chromatography employing benzene/EtOAc as eluent gave the analytically pure diastereoisomers. Detailed NMR-spectroscopy through HMBC and NOESY experiments of the two diastereoisomers of compound **8a** led us to establish the less polar compound (R_f=0.49, benzene/EtOAc, 7:3, v/v) as the trans-isomer while the slightly more polar compound (R_f=0.47, benzene/EtOAc, 7:3, v/v) was the cis-isomer.

Aiming to investigate the synthetic utility of the generated 2-pyridone system, we decided to perform spiroannulation reactions at the exocyclic C–C double bond by exploiting the well-established versatility of 1,3-dipolar cycloadditions.[10] Although two regioisomers of the product can result through cycloaddition, treatment of compound **5b** with phenyl nitrile oxide yielded only a single product as evident from the crude ^1H and ^{13}C NMR. The structure of the product was established as **9b** (Scheme 2) implying that this reaction proceeded in a highly regioselective manner. Such regioselective 1,3-dipolar additions have previously been documented.[10f,11] In view of this observation the general applicability of this cycloaddition was investigated by subjecting compounds **5b**, **6c**, and **7f** to similar reactions with several substituted nitrile oxides. Gratifyingly all products **9–12b**, **13–17c**, **18–21f** were afforded



Scheme 2. Reagents and conditions: (i) R^2CNO, Et_3N, dry Et_2O, −78 °C to rt, 6 h.

regioselectively in excellent yields. The spectral analysis of these products showed a high degree of stereoselectivity too. From NOESY and COSY studies with a representative product **21f**, the stereochemistry of these products was found to result from the attack of the dipole *syn* to the hydrogen at the 4-position of the 2-pyridone. In order to resolve the issue of selectivity unambiguously the X-ray crystallographic analysis of a single crystal of **21f** was performed (Fig. 1).[12] This clearly showed that the pyridone and isoxazoline rings are almost perpendicular to one another and the relative configuration is the one shown in Scheme 2. This unusual stereoselectivity is probably related to the bulkiness of the phenyl or the substituted phenyl group in the dipolarophile.

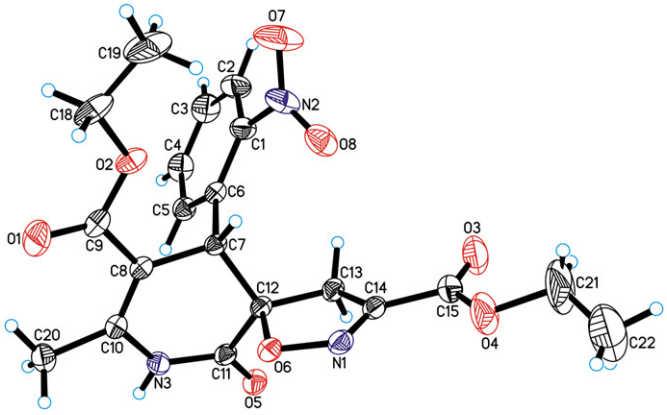


Figure 1. ORTEP diagram of compound **21f** showing atomic numbering scheme (all hydrogens are omitted for clarity).

3. Conclusions

The present work demonstrates a facile approach to the synthesis of substituted 3-methylene-2-pyridones. The 1,3-dipolar cycloadditions of these substrates with nitrile oxides occur in highly regio- and stereo-selective fashion to provide a new spirocyclic system containing substituted 2-pyridone and isoxazoline rings.

4. Experimental

4.1. General

Melting points are uncorrected and were determined in capillary tubes on an apparatus containing silicon oil. IR spectra were recorded using a Perkin Elmer's Spectrum RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker DPX-200 FT or Bruker Avance DRX-300 spectrometer, using TMS as an internal standard (chemical shifts in δ). The ESMS and FABMS were recorded on MICROMASS Quadro-II LCMS and JEOL SX/102/DA 6000 systems, respectively. Elemental analyses were performed on a Carlo Erba's 108 or an Elementar's Vario EL III microanalyzer.

4.2. General procedure for the preparation of compounds 3–4a–h as exemplified for 3a

To a stirred solution of acetate **2a** (1.5 g, 7.5 mmol) in a mixture of THF/water (16 mL, 1:1, v/v), DABCO (1.25 g, 11.2 mmol) was added and stirred for 15 min at room temperature. Thereafter, acetyl acetone (0.92 mL, 9.2 mmol) was added dropwise and the reaction was stirred for 2 h. After completion of the reaction as monitored by TLC, THF was evaporated in vacuo and the residue was extracted with EtOAc (3×50 mL) and water (70 mL). The organic layers were combined and washed with brine (50 mL), dried over Na_2SO_4, and concentrated to yield the crude product. Purification via silica gel column chromatography using hexane/EtOAc (9:1, v/v) afforded 1.57 g (87%) pure **3a** as a white solid.

4.2.1. 2-(2-Acetyl-3-oxo-1-phenylbutyl)acrylonitrile (3a)

Mp 75–78 °C, R_f=0.51 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1698 (CO), 2226 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.95 (s, 3H, $COCH_3$), 2.33 (s, 3H, $COCH_3$), 4.40 (d, 1H, J=12.0 Hz, CH), 4.67 (d, 1H, J=12.0 Hz), 5.89 (s, 1H, =CHH), 5.94 (s, 1H, =CHH), 7.28–7.38 (m, 5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=29.7, 30.5, 49.5, 71.5, 117.2, 124.0, 127.8, 128.5, 129.5, 132.1, 136.9, 200.5, 200.9; mass (ES^+) m/z=242.2 (M^++1, 30%). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.52; H, 6.11; N, 5.89.

4.2.2. 2-[2-Acetyl-1-(4-methylphenyl)-3-oxobutyl]-acrylonitrile (3b)

Yield: 85% (1.05 g from 0.93 g) as a white solid, mp 116–117 °C, R_f=0.40 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1699 (CO), 2226 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.95 (s, 3H, $COCH_3$), 2.32 (s, 6H, $COCH_3$ and $ArCH_3$), 4.36 (d, 1H, J=12.0 Hz, CH), 4.64 (d, 1H, J=12.0 Hz, CH), 5.87 (s, 1H, =C*H*H), 5.91 (s, 1H, =CH*H*), 7.14 (d, 2H, J=9.0 Hz, ArH), 7.17 (d, 2H, J=9.0 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=21.1, 29.7, 30.5, 49.1, 71.5, 117.2, 124.3, 127.7, 130.1, 131.8, 133.8, 138.2, 200.6, 201.0; mass (ES^+) m/z=256.2 (M^++1, 100%). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.33; H, 6.62; N, 5.78.

4.2.3. 2-[2-Acetyl-1-(4-chlorophenyl)-3-oxobutyl]-acrylonitrile (3c)

Yield: 88% (1.63 g from 1.5 g) as a white solid, mp 102–103 °C, R_f=0.52 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1698 (CO), 2227 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.98 (s, 3H, $COCH_3$), 2.33 (s, 3H, $COCH_3$), 4.39 (d, 1H, J=11.9 Hz, CH), 4.62 (d, 1H, J=11.9 Hz, CH), 5.91 (s, 1H, =C*H*H), 5.94 (s, 1H, =CH*H*), 7.23 (d, 2H, J=8.5 Hz, ArH), 7.33 (d, 2H, J=8.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=29.9, 30.6, 48.8, 71.4, 117.0, 123.5, 129.2, 129.7, 132.5, 134.5, 135.5, 200.1, 200.5; mass (ES^+) m/z=276.2 (M^++1, 100%), 278.2 (M^++3). Anal. Calcd for $C_{15}H_{15}ClNO_2$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.29; H, 5.01; N, 4.91.

*4.2.4. 2-[2-Acetyl-1-(4-fluorophenyl)-3-oxobutyl]-acrylonitrile (**3d**)*

Yield: 67% (0.79 g from 1.0 g) as a white solid, mp 113–114 °C, R_f=0.38 (hexane/EtOAc, 80:20); ν_{max} (KBr) 1698 (CO), 2229 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.97 (s, 3H, $COCH_3$), 2.33 (s, 3H, $COCH_3$), 4.40 (d, 1H, J=12.0 Hz, CH), 4.62 (d, 1H, J=12.0 Hz, CH), 5.90 (s, 1H, =C*H*H), 5.93 (s, 1H, =CH*H*), 7.01–7.09 (m, 2H, ArH), 7.24–7.31 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=30.1, 30.9, 49.0, 71.9, 116.6, 117.0, 117.4, 124.0, 129.8, 130.0, 132.6, 133.0, 200.6, 201.0; mass (ES^+) m/z=260 (M^++1, 80%), 282 (M^++Na, 100%). Anal. Calcd for $C_{15}H_{14}FNO_2$: C, 69.49; H, 5.44; N, 5.40. Found: C, 69.74; H, 5.60; N, 5.29.

*4.2.5. 2-[2-Acetyl-1-(2-chlorophenyl)-3-oxobutyl]-acrylonitrile (**3e**)*

Yield: 82% (0.78 g from 0.81 g) as a white solid, mp 58–59 °C, R_f=0.41 (hexane/EtOAc, 80:20); ν_{max} (KBr) 1705 (CO), 2223 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.95 (s, 3H, $COCH_3$), 2.36 (s, 3H, $COCH_3$), 4.71 (d, 1H, J=12.0 Hz, CH), 5.09 (d, 1H, J=12.0 Hz), 5.94 (s, 1H, =C*H*H), 6.11 (s, 1H, =CH*H*), 7.25–7.45 (m, 4H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=28.4, 31.4, 44.8, 71.5, 117.0, 121.8, 128.3, 128.6, 130.0, 131.0, 134.1, 134.3, 134.5, 200.5, 201.1; mass (ES^+) m/z=276.1 (M^++1, 100%), 278.1 (M^++3, 30%). Anal. Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.55; H, 5.04; N, 5.22.

*4.2.6. 2-[2-Acetyl-1-(2-nitrophenyl)-3-oxobutyl]-acrylonitrile (**3f**)*

Yield: 65% (0.79 g from 1.01 g) as a white solid, mp 133–134 °C, R_f=0.20 (hexane/EtOAc, 80:20); ν_{max} (KBr) 1706 (CO), 2227 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.98 (s, 3H, $COCH_3$), 2.35 (s, 3H, $COCH_3$), 4.70 (d, 1H, J=12.0 Hz, CH), 5.21 (d, 1H, J=12.0 Hz, CH), 6.02 (s, 1H, =C*H*H), 6.19 (s, 1H, =CH*H*), 7.45–7.65 (m, 3H, ArH), 7.88 (d, 1H, J=7.5 Hz, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=29.3, 31.0, 42.6, 72.0, 117.0, 121.4, 125.8, 128.9, 129.6, 131.1, 133.8, 135.7, 150.3, 199.9, 200.3; mass (FAB^+) m/z=287 (M^++1, 25%). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: C, 63.09; H, 5.05; N, 9.66.

*4.2.7. 2-[2-Acetyl-1-(2-fluorophenyl)-3-oxobutyl]-acrylonitrile (**3g**)*

Yield: 91% (1.61 g from 1.77 g) as a white solid, mp 92–94 °C, R_f=0.35 (hexane/EtOAc, 70:20); ν_{max} (KBr) 1696 (CO), 2226 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.00 (s, 3H, $COCH_3$), 2.35 (s, 3H, $COCH_3$), 4.73 (d, 1H, J=12.1 Hz, CH), 4.80 (d, 1H, J=12.1 Hz, CH), 5.93 (s, 1H, =C*H*H), 6.00 (s, 1H, =CH*H*), 7.05–7.18 (m, 2H, ArH), 7.27–7.34 (m, 2H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=28.8, 30.8, 41.9, 70.5, 116.3, 116.5, 116.9, 122.4, 124.0, 124.2, 125.1, 125.2, 128.7, 130.2, 130.3, 133.2, 158.8, 162.0, 200.1, 200.7; mass (ES^+) m/z=260.2 (M^++1, 100%). Anal. Calcd for $C_{15}H_{14}FNO_2$: C, 69.49; H, 5.44; N, 5.40. Found: C, 69.77; H, 5.23; N, 5.55.

*4.2.8. 2-[2-Acetyl-1-(2,6-dichlorophenyl)-3-oxobutyl]-acrylonitrile (**3h**)*

Yield: 78% (1.00 g from 1.26 g) as colorless oil, R_f=0.40 (hexane/EtOAc, 70:30); ν_{max} (neat) 1698 (CO), 2226 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=2.02 (s, 3H, $COCH_3$), 2.37 (s, 3H, $COCH_3$), 5.27 (d, 1H, J=12.1 Hz, CH), 5.59 (d, 1H, J=12.1 Hz, CH), 5.69 (s, 1H, =C*H*H), 6.05 (s, 1H, =CH*H*), 7.15–7.42 (m, 3H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=29.7, 30.0, 41.9, 68.7, 117.6, 121.8, 129.3, 130.1, 130.3, 133.0, 133.7, 135.5, 137.2, 200.1, 200.3; mass (ES^+) m/z=311.2 (M^++1, 100%). Anal. Calcd for $C_{15}H_{13}Cl_2NO_2$: C, 58.08; H, 4.22; N, 4.52. Found: C, 58.44; H, 4.10; N, 4.25.

*4.2.9. Ethyl 2-acetyl-4-cyano-3-phenylpent-4-enoate (**4a**) (diastereoisomeric mixture, 2:1)*

Yield: 95% (0.89 g from 0.75 g) as a white solid, mp 73–74 °C, R_f=0.65 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1703 (CO), 1737 (CO_2Et), 2225 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=0.97 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.31 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.07 (s, 3H, $COCH_3$), 2.38 (s, 3H, $COCH_3$), 3.90–3.98 (m, 2H, OCH_2CH_3), 4.25 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.34–4.46 (m, 4H, 2×CHAr and 2×CHCO), 5.89 (s, 1H, =C*H*H), 5.90 (s, 1H, =C*H*H), 5.94 (s, 1H, =CH*H*), 5.96 (s, 1H, =CH*H*), 7.28–7.37 (m, 10H, 2×5ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.7, 14.1, 30.4, 30.8, 48.9, 49.4, 61.9, 62.1, 62.2, 62.7, 117.3, 123.9, 124.2, 127.0, 128.2, 128.3, 129.1, 129.3, 131.6, 132.4, 137.1, 137.5, 166.2, 167.9, 199.9, 200.0; mass (ES^+) m/z=272 (M^++1, 33%). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.16; H, 6.15; N, 5.21.

*4.2.10. Ethyl 2-acetyl-4-cyano-3-(4-methylphenyl)pent-4-enoate (**4b**) (diastereoisomeric mixture, 3:2)*

Yield: 85% (0.78 g from 0.69 g) as yellow oil, R_f=0.47 (hexane/EtOAc, 80:20); ν_{max} (neat) 1720 (CO), 1742 (CO_2Et), 2224 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.01 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.27–1.33 (m, 3H, OCH_2CH_3), 2.07 (s, 3H, $COCH_3$), 2.32 (s, 6H, 2×$ArCH_3$), 2.38 (s, 3H, $COCH_3$), 3.96 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.20–4.35 (m, 3H, OCH_2 merged with CH), 4.37–4.44 (m, 3H, 2×ArCH and CH), 5.87 (s, 1H, =C*H*H), 5.89 (s, 1H, =C*H*H), 5.93 (s, 1H, =CH*H*), 5.95 (d, 1H, =CH*H*), 7.13–7.22 (m, 8H, 2×4ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.8, 14.1, 30.3, 30.7, 48.5, 49.1, 61.9, 62.2, 62.5, 117.4, 124.2, 124.5, 127.6, 129.7, 130.0, 131.3, 132.0, 134.0, 134.5, 137.9, 138.1, 166.3, 168.0, 200.0, 200.1; mass (ES^+) m/z=286.2 (M^++1, 90%). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.60; H, 6.80; N, 5.02.

*4.2.11. Ethyl 2-acetyl-3-(4-chlorophenyl)-4-cyanopent-4-enoate (**4c**) (diastereoisomeric mixture, 3:2)*

Yield: 89% (1.17 g from 1.00 g) as yellow oil, R_f=0.50 (hexane/EtOAc, 80:20); ν_{max} (neat) 1721 (CO), 1744 (CO_2Et), 2225 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.02 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.30 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.09 (s, 3H, $COCH_3$), 2.37 (s, 3H, $COCH_3$),

3.96 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 4.22 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 4.34 (s, 2H, 2×ArCH), 4.37 (s, 2H, 2×COCH), 5.90 (s, 1H, =CH), 5.91 (s, 1H, =CH), 5.94 (s, 1H, =CH), 5.95 (s, 1H, =CH), 7.22–7.27 (m, 4H, 2×2ArH), 7.29–7.32 (m, 4H, 2×2ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=14.1, 14.4, 30.8, 31.1, 48.5, 49.0, 62.5, 62.8, 117.4, 123.7, 124.1, 129.5, 129.6, 129.8, 132.3, 133.1, 134.5, 134.6, 136.0, 136.4, 166.3, 166.9, 199.8, 200.0; mass (ES^+) m/z=306.1 (M^++1, 100%), 308.1 (M^++3, 35%). Anal. Calcd for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.27; N, 4.58. Found: C, 63.11; H, 5.40; N, 4.47.

4.2.12. Ethyl 2-acetyl-4-cyano-3-(4-fluorophenyl)pent-4-enoate (**4d**) (diastereoisomeric mixture, 1:1)

Yield: 78% (0.62 g from 0.50 g) as colorless oil, R_f=0.49 (hexane/EtOAc, 80:20); ν_{max} (neat) 1720 (CO), 1744 (CO_2Et), 2225 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.01 (t, 3H, J=7.1 Hz, OCH$_2$CH_3), 1.30 (t, 3H, J=7.1 Hz, OCH$_2$CH_3), 2.08 (s, 3H, COCH$_3$), 2.37 (s, 3H, COCH$_3$), 3.92–4.00 (m, 2H, OCH_2CH$_3$), 4.24 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 4.34 (s, 2×1H, ArCH), 4.37 (s, 2×1H, COCH), 5.90 (s, 1H, =CHH), 5.91 (s, 1H, =CHH), 5.94 (s, 1H, =CHH), 5.95 (d, 1H, =CHH), 7.01–7.06 (m, 4H, 2×2ArH), 7.25–7.32 (m, 4H, 2×2ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=14.1, 14.4, 30.7, 31.1, 48.4, 48.9, 62.4, 62.6, 62.7, 63.0, 116.1, 116.4, 116.6, 116.8, 117.5, 124.0, 124.3, 129.8, 129.9, 132.0, 132.8, 133.1, 133.2, 133.6, 133.7, 160.3, 165.2, 166.4, 167.0, 199.9, 200.1; mass (ES^+) m/z=290.2 (M^++1, 100%). Anal. Calcd for $C_{16}H_{16}FNO_3$: C, 66.43; H, 5.57; N, 4.84. Found: C, 66.54; H, 5.66; N, 5.02.

4.2.13. Ethyl 2-acetyl-3-(2-chlorophenyl)-4-cyanopent-4-enoate (**4e**) (diastereoisomeric mixture, 1:1)

Yield: 88% (1.20 g from 1.26 g) as colorless oil, R_f=0.48 (hexane/EtOAc, 80:20); ν_{max} (neat) 1703 (CO), 1733 (CO_2Et), 2223 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.97 (t, 3H, J=7.1 Hz, OCH$_2$CH_3), 1.31 (t, 3H, J=7.1 Hz, OCH$_2$CH_3), 2.13 (s, 3H, COCH$_3$), 2.40 (s, 3H, COCH$_3$), 3.95 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 4.24 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 4.44 (d, 1H, J=11.9 Hz, CH), 4.48 (d, 1H, J=11.9 Hz, CH), 4.98 (d, 1H, J=11.9 Hz, CH), 5.04 (d, 1H, J=11.9 Hz, CH), 5.93 (s, 1H, =CHH), 5.94 (s, 1H, =CHH), 6.08 (s, 1H, =CHH), 6.10 (s, 1H, =CHH), 7.20–7.35 (m, 6H, 2×3ArH), 7.36–7.43 (m, 2H, 2×1ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.7, 14.1, 29.6, 30.6, 44.0, 44.8, 50.3, 61.9, 62.0, 62.1, 62.4, 116.9, 121.8, 122.0, 127.4, 127.7, 127.8, 128.0, 129.2, 129.4, 130.4, 130.7, 133.3, 134.0, 134.2, 134.4, 134.9, 166.0, 166.9, 199.3, 199.6; mass (ES^+) m/z=306.2 (M^++1, 100%), 308.2 (M^++3, 35%). Anal. Calcd for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.27; N, 4.58. Found: C, 63.07; H, 5.29; N, 4.70.

4.2.14. Ethyl 2-acetyl-4-cyano-3-(2-nitrophenyl)pent-4-enoate (**4f**) (diastereoisomeric mixture, 3:2)

Yield: 70% (1.35 g from 1.50 g) as a white solid, mp 82–83 °C, R_f=0.50 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1723 (CO), 1736 (CO_2Et), 2226 (CN) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=0.96 (t, 3H, J=7.1 Hz, OCH$_2$CH_3), 1.31 (t, 3H, J=7.1 Hz, OCH$_2$CH_3), 2.12 (s, 3H, COCH$_3$), 2.39 (s, 3H, COCH$_3$), 3.91 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 4.25 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 4.41 (d, 1H, J=11.8 Hz, ArCH), 4.47 (d, 1H, J=11.8 Hz, ArCH), 5.07 (d, 2H, J=11.8 Hz, 2×COCH), 6.05 (s, 1H, =CH), 6.06 (s, 1H, =CH), 6.24 (s, 1H, =CH), 6.28 (s, 1H, =CH), 7.42–7.48 (m, 2H, 2×1ArH), 7.56–7.65 (m, 4H, 2×2ArH), 7.83–7.89 (m, 2H, 2×1ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=13.6, 14.1, 29.7, 30.6, 41.7, 42.2, 62.4, 62.6, 62.8, 117.0, 120.9, 121.2, 125.1, 125.4, 128.0, 128.6, 129.0, 131.7, 131.9, 133.3, 135.2, 136.0, 150.1, 166.3, 198.8, 199.0; mass (ES^+) m/z=317.1 (M^++1, 92%), 339.1 (M^++Na, 48%). Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 60.93; H, 5.12; N, 9.08.

4.2.15. Ethyl 2-acetyl-4-cyano-3-(2-fluorophenyl)pent-4-enoate (**4g**) (diastereoisomeric mixture, 1:1)

Yield: 85% (2.25 g from 2.00 g) as colorless oil, R_f=0.47 (hexane/EtOAc, 80:20); ν_{max} (neat) 1696 (CO), 1726 (CO_2Et), 2224 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=0.98 (t, 3H, J=7.1 Hz, OCH$_2$CH_3), 1.31 (t, 3H, J=7.1 Hz, OCH$_2$CH_3), 2.15 (s, 3H, COCH$_3$), 2.39 (s, 3H, COCH$_3$), 3.96 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 4.25 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 4.46–4.52 (m, 2H, 2×CH), 4.67–4.76 (m, 2H, 2×CH), 5.92 (s, 2H, 2×=CHH), 5.99 (s, 2H, 2×=CHH), 7.03–7.24 (m, 4H, ArH), 7.25–7.36 (m, 4H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=14.0, 14.4, 30.4, 30.8, 41.7, 41.8, 42.5, 42.6, 61.4, 61.8, 62.4, 62.7, 116.2, 116.4, 116.6, 116.9, 117.3, 117.4, 122.8, 123.0, 124.9, 125.0, 125.2, 125.3, 128.9, 130.1, 130.2, 130.4, 132.9, 133.6, 166.3, 167.1, 199.7, 200.0; mass (ES^+) m/z=290.1 (M^++1, 100%). Anal. Calcd for $C_{16}H_{16}FNO_3$: C, 66.43; H, 5.57; N, 4.84. Found: C, 66.74; H, 5.34; N, 4.95.

4.2.16. Ethyl 2-acetyl-4-cyano-3-(2,6-dichlorophenyl)pent-4-enoate (**4h**) (diastereoisomeric mixture, 3:2)

Yield: 90% (1.13 g from 1.00 g) as colorless oil, R_f=0.51 (hexane/EtOAc, 80:20); ν_{max} (neat) 1722 (CO), 1742 (CO_2Et), 2225 (CN) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=0.97 (t, 3H, J=7.1 Hz, OCH$_2$CH_3), 1.32 (t, 3H, J=7.1 Hz, OCH$_2$CH_3), 2.15 (s, 3H, COCH$_3$), 2.41 (s, 3H, COCH$_3$), 3.91 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 4.29 (q, 2H, J=7.1 Hz, OCH_2CH$_3$), 4.98 (d, 1H, J=11.3 Hz, CH), 5.08 (d, H, J=11.6 Hz, CH), 5.56 (d, 2H, J=11.3 Hz, 2×CH), 5.67–5.80 (m, 2H, 2×=CHH), 6.02–6.07 (m, 2H, 2×=CHH), 7.13–7.39 (m, 6H, 2×3ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=14.0, 14.4, 29.8, 30.6, 41.5, 42.8, 59.6, 60.8, 62.3, 62.9, 117.7, 118.0, 122.0, 122.5, 129.1, 129.7, 130.0, 130.2, 130.4, 131.0, 132.9, 133.1, 133.7, 135.0, 136.1, 137.7, 166.4, 167.5, 199.7, 200.1; mass (ES^+) m/z=340.0 (M^++1, 100%). Anal. Calcd for $C_{16}H_{15}Cl_2NO_3$: C, 56.49; H, 4.44; N, 4.12. Found: C, 56.52; H, 4.22; N, 4.39.

4.3. General procedure for the preparation of **5–6a–f** as exemplified for **5a**

To a flask containing compound **3a** (0.5 g, 2.06 mmol), 3.0 mL of TFA/H_2SO_4 (4:1, v/v) was added and stirred

vigorously for 3 min at room temperature. The reaction mixture was quenched by pouring into crushed ice and stirring vigorously with a glass rod. The product was extracted with EtOAc (3×25 mL). The organic layer was then neutralized with saturated Na_2CO_3 solution, washed with 50 mL brine, and concentrated in vacuo. Purification by column chromatography on silica gel (60–120 mesh, deactivated by adding 12 mL of water to 100 g of silica gel) using hexane/EtOAc (85:15 v/v) as eluent yielded 0.34 g (68%) of pure **5a** as a white solid.

*4.3.1. 5-Acetyl-6-methyl-3-methylene-4-phenyl-3,4-dihydropyridin-2(1H)-one (**5a**)*

Mp 150–152 °C, R_f=0.53 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1637 (CONH), 1670 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.13 (s, 3H, CH_3), 2.40 (s, 3H, $COCH_3$), 4.78 (s, 1H, CH), 5.71 (s, 1H, =C*H*H), 6.24 (s, 1H, =CH*H*), 7.19–7.32 (m, 5H, ArH), 8.75 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=19.8, 29.9, 47.5, 115.5, 125.7, 126.8, 127.5, 129.3, 139.6, 141.1, 144.9, 164.9, 197.6; mass (ES^+) *m/z*=242.2 (M^++1, 100%). Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.76; H, 6.24; N, 5.98.

*4.3.2. 5-Acetyl-6-methyl-3-methylene-4-(4-methylphenyl)-3,4-dihydropyridin-2(1H)-one (**5b**)*

Yield: 70% (0.14 g from 0.20 g) as a white solid, mp 158–159 °C, R_f=0.54 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1640 (CONH), 1690 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.12 (s, 3H, $ArCH_3$), 2.30 (s, 3H, CH_3), 2.39 (s, 3H, $COCH_3$), 4.74 (s, 1H, CH), 5.69 (s, 1H, =C*H*H), 6.22 (s, 1H, =CH*H*), 7.09 (s, 4H, ArH), 8.77 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=19.7, 21.1, 29.9, 47.2, 115.6, 125.4, 126.7, 129.9, 137.2, 138.1, 139.9, 144.8, 165.0, 197.7; mass (ES^+) *m/z*=256.1 (M^++1, 72%). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.38; H, 6.91; N, 5.50.

*4.3.3. 5-Acetyl-4-(4-chlorophenyl)-6-methyl-3-methylene-3,4-dihydropyridin-2(1H)-one (**5c**)*

Yield: 64% (0.62 g from 0.95 g) as a white solid, mp 179–180 °C, R_f=0.30 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1633 (CONH), 1677 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.16 (s, 3H, CH_3), 2.41 (s, 3H, $COCH_3$), 4.79 (s, 1H, CH), 5.72 (s, 1H, =C*H*H), 6.27 (s, 1H, =CH*H*), 7.15 (d, 2H, *J*=8.4 Hz, ArH), 7.27 (d, 2H, *J*=8.4 Hz, ArH), 8.88 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=19.8, 30.0, 46.7, 115.4, 126.0, 128.2, 129.3, 133.3, 139.2, 139.6, 145.2, 164.9, 197.2; mass (ES^+) *m/z*=276.2 (M^++1, 100%), 278.2 (M^++3, 30%). Anal. Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.44; H, 5.14; N, 4.95.

*4.3.4. 5-Acetyl-4-(4-fluorophenyl)-6-methyl-3-methylene-3,4-dihydropyridin-2(1H)-one (**5d**)*

Yield: 61% (0.37 g from 0.6 g) as a white solid, mp 130–131 °C, R_f=0.25 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1634 (CONH), 1701 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.16 (s, 3H, CH_3), 2.42 (s, 3H, $COCH_3$), 4.79 (s, 1H, CH), 5.73 (s, 1H, =C*H*H), 6.26 (s, 1H, =CH*H*), 6.96–7.02 (m, 2H, ArH), 7.16–7.21 (m, 2H, ArH), 8.97 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=19.9, 30.0, 46.6, 115.6, 116.0, 116.2, 125.9, 128.4, 128.5, 136.7, 136.8, 144.9, 160.5, 164.9, 197.4; mass (ES^+) *m/z*=260.1 (M^++1, 85%). Anal. Calcd for $C_{15}H_{14}FNO_2$: C, 69.49; H, 5.44; N, 5.40. Found: C, 69.60; H, 5.41; N, 5.33.

*4.3.5. 5-Acetyl-4-(2-chlorophenyl)-6-methyl-3-methylene-3,4-dihydropyridin-2(1H)-one (**5e**)*

Yield: 67% (0.52 g from 0.78 g) as a white solid, mp 150–151 °C, R_f=0.40 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1633 (CONH), 1680 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.05 (s, 3H, CH_3), 2.41 (s, 3H, $COCH_3$), 5.43 (d, 1H, *J*=0.9 Hz, CH), 6.00 (s, 1H, =C*H*H), 6.30 (s, 1H, =CH*H*), 7.19 (t, 3H, *J*=1.9 Hz, ArH), 7.39–7.42 (m, 1H, ArH), 8.88 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=19.7, 29.4, 42.9, 115.1, 126.9, 128.0, 128.7, 130.6, 132.8, 137.7, 138.6, 145.2, 164.4, 197.7; mass (ES^+) *m/z*=276.1 (M^++1, 100%), 278.2 (M^++3, 25%). Anal. Calcd for $C_{15}H_{14}ClNO_2$: C, 65.34; H, 5.12; N, 5.08. Found: C, 65.59; H, 4.96; N, 5.08.

*4.3.6. 5-Acetyl-4-(2-nitrophenyl)-6-methyl-3-methylene-3,4-dihydropyridin-2(1H)-one (**5f**)*

Yield: 35% (0.05 g from 0.2 g) as a white solid, mp 135–136 °C, R_f=0.15 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1627 (CONH), 1698 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.16 (s, 3H, CH_3), 2.43 (s, 3H, $COCH_3$), 5.81 (s, 1H, CH), 5.86 (s, 1H, =C*H*H), 6.31 (s, 1H, =CH*H*), 7.32–7.42 (m, 2H, ArH), 7.50 (q, 1H, *J*=1.3 Hz, ArH), 7.82 (dd, 1H, J_1=1.2 Hz, J_2=8.0 Hz, ArH), 8.08 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=19.8, 30.0, 40.2, 115.1, 125.3, 127.8, 128.3, 128.5, 133.4, 135.5, 137.3, 145.5, 148.9, 164.4, 197.0; mass (ES^+) *m/z*=287.1 (M^++1, 100%). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.79. Found: 63.07; H, 5.11; N, 9.60.

4.3.7. 2-Methylene-3-(2-nitrophenyl)-5-oxo-hexanoic acid (side product)

Yield: 20% (0.04 g from 0.2 g) as a white solid, mp 129–130 °C, R_f=0.12 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1626 (CO_2H), 1695 ($COCH_3$) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.18 (s, 3H, $COCH_3$), 3.06 (d, 2H, *J*=7.4 Hz, CH_2CO), 5.00 (t, 2H, *J*=7.4 Hz, CHAr), 5.70 (d, 1H, *J*=1.2 Hz, =C*H*H), 6.50 (s, 1H, =CH*H*), 7.28–7.40 (m, 2H, ArH), 7.50–7.55 (m, 1H, ArH), 7.85 (dd, 1H, J_1=0.8 Hz, J_2=7.4 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=29.4, 36.7, 47.8, 124.7, 125.7, 127.5, 129.1, 132.7, 136.4, 141.3, 149.5, 168.0, 205.8; mass (ES^+) *m/z*=264.1 (M^++1, 50%). Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.48; H, 5.13; N, 5.19.

*4.3.8. 5-Acetyl-4-(2-fluorophenyl)-6-methyl-3-methylene-3,4-dihydropyridin-2(1H)-one (**5g**)*

Yield: 45% (0.20 g from 0.45 g) as a white solid, mp 139–141 °C, R_f=0.24 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1637 (CONH), 1692 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.09 (s, 3H, CH_3), 2.42 (s, 3H, $COCH_3$), 5.21 (s, 1H, CH), 5.85 (s, 1H, =C*H*H), 6.31 (s, 1H, =CH*H*), 7.03–7.14

(m, 3H, ArH), 7.19–7.25 (m, 1H, ArH), 8.15 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=19.7, 29.5, 40.0, 114.0, 116.1, 116.4, 124.8, 124.9, 127.0, 127.7, 127.8, 128.3, 128.5, 129.3, 137.9, 145.7, 158.6, 161.9, 164.7, 197.4; mass (ES^+) *m/z*=260.1 (M^++1, 100%). Anal. Calcd for $C_{15}H_{14}FNO_2$: C, 69.49; H, 5.44; N, 5.40. Found: C, 69.67; H, 5.19; N, 5.22.

*4.3.9. 5-Acetyl-4-(2,6-dichlorophenyl)-6-methyl-3-methylene-3,4-dihydropyridin-2(1H)-one (**5h**)*

Yield: 43% (0.35 g from 0.83 g) as a white solid, mp 89–91 °C, R_f=0.38 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1633 (CONH), 1677 (CO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=2.08 (s, 3H, CH_3), 2.21 (s, 3H, $COCH_3$), 5.44 (d, 1H, *J*=2.3 Hz, CH), 5.87 (d, 1H, *J*=1.7 Hz, =C*H*H), 6.50 (d, 1H, *J*=2.9 Hz, =CH*H*), 7.14 (t, 1H, *J*=8.0 Hz, ArH), 7.32 (d, 2H, *J*=8.0 Hz, ArH), 7.84 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=20.0, 30.6, 42.3, 114.9, 127.1, 129.2, 129.8, 135.8, 136.4, 140.2, 141.2, 163.4, 198.6; mass (ES^+) *m/z*=310.2 (M^++1, 100%). Anal. Calcd for $C_{15}H_{13}Cl_2NO_2$: C, 58.08; H, 4.22; N, 4.52. Found: C, 57.86; H, 4.44; N, 4.65.

*4.3.10. Ethyl 2-methyl-5-methylene-6-oxo-4-phenyl-1,4,5,6-tetrahydropyridine-3-carboxylate (**6a**)*

Yield: 64% (0.33 g from 0.52 g) as a white solid, mp 140–142 °C, R_f=0.50 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1632 (CONH), 1704 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.20 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 2.44 (s, 3H, CH_3), 4.13 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 4.89 (s, 1H, CH), 5.69 (d, 1H, *J*=0.6 Hz, =C*H*H), 6.32 (s, 1H, =CH*H*), 7.20–7.31 (m, 5H, ArH), 8.87 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.5, 19.4, 46.6, 60.6, 107.9, 126.6, 127.1, 127.3, 129.1, 139.7, 143.0, 145.5, 165.6, 166.7; mass (ES^+) *m/z*=272.1 (M^++1, 100%). Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 71.10; H, 6.33; N, 5.27.

*4.3.11. Ethyl 2-methyl-5-methylene-4-(4-methylphenyl)-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (**6b**)*

Yield: 67% (0.14 g from 0.2 g) as a white solid, mp 158–159 °C, R_f=0.51 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1640 (CONH), 1698 (CO_2Et) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.20 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 2.29 (s, 3H, $ArCH_3$), 2.41 (s, 3H, CH_3), 4.12 (q, 1H, *J*=7.1 Hz, OCH_2CH_3), 4.83 (s, 1H, CH), 5.66 (s, 1H, =C*H*H), 6.28 (s, 1H, =CH*H*), 7.08 (s, 4H, ArH), 7.85 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.3, 19.2, 21.1, 46.0, 60.3, 107.8, 126.1, 126.7, 129.5, 136.6, 139.6, 139.8, 145.0, 165.3, 166.7; mass (ES^+) *m/z*=286.3 (M^++1, 100%). Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.50; H, 6.66; N, 5.09.

*4.3.12. Ethyl 4-(4-chlorophenyl)-2-methyl-5-methylene-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (**6c**)*

Yield: 62% (0.25 g from 0.41 g) as a white solid, mp 159–160 °C, R_f=0.45 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1634 (CONH), 1705 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.19 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 2.42 (s, 3H, CH_3), 4.11 (q, 2H, *J*=7.1 Hz, OCH_2CH_3), 4.83 (s, 1H, CH), 5.67 (s, 1H, =C*H*H), 6.30 (s, 1H, =CH*H*), 7.14 (d, 2H, *J*=8.5 Hz, ArH), 7.23 (d, 2H, *J*=8.5 Hz, ArH), 8.81 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.3, 19.2, 45.8, 60.5, 107.2, 126.7, 128.2, 129.0, 132.9, 139.1, 141.3, 145.6, 165.1, 166.4; mass (ES^+) *m/z*=306.3 (M^++1, 100%), 308.3 (M^++3, 30%). Anal. Calcd for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.27; N, 4.58. Found: C, 63.00; H, 5.11; N, 4.49.

*4.3.13. Ethyl 4-(4-fluorophenyl)-2-methyl-5-methylene-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (**6d**)*

Yield: 56% (0.39 g from 0.69 g) as a white solid, mp 145–146 °C, R_f=0.49 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1631 (CONH), 1704 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.19 (t, 3H, OCH_2CH_3), 2.42 (s, 3H, CH_3), 4.08–4.15 (m, 2H, OCH_2CH_3), 4.85 (s, 1H, CH), 5.66 (d, 1H, *J*=0.6 Hz, =C*H*H), 6.30 (s, 1H, =CH*H*), 6.91–6.98 (m, 2H, ArH), 7.14–7.19 (m, 2H, ArH), 7.76 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.3, 19.1, 45.6, 60.4, 107.5, 115.5, 115.8, 126.1, 126.5, 128.4, 138.4, 139.3, 145.5, 160.3, 163.5, 165.3, 166.5; mass (ES^+) *m/z*=290.4 (M^++1, 100%). Anal. Calcd for $C_{16}H_{16}FNO_3$: C, 66.43; H, 5.57; N, 4.84. Found: C, 66.28; H, 5.66; N, 4.77.

*4.3.14. Ethyl 4-(2-chlorophenyl)-2-methyl-5-methylene-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (**6e**)*

Yield: 62% (0.37 g from 0.60 g) as a white solid, mp 140–141 °C, R_f=0.45 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1680 (CONH), 1704 (CO_2Et) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ=1.12 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 2.48 (s, 3H, CH_3), 4.00–4.08 (m, 2H, OCH_2CH_3), 5.54 (d, 1H, *J*=1.1 Hz, CH), 5.94 (s, 1H, =CH), 6.35 (s, 1H, =CH), 7.11–7.20 (m, 3H, ArH), 7.37–7.39 (m, 1H, ArH), 8.79 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.1, 19.0, 42.1, 60.3, 107.2, 127.3, 127.5, 128.1, 128.2, 130.2, 132.9, 138.0, 140.8, 145.8, 164.5, 166.3; mass (ES^+) *m/z*=306.2 (M^++1, 100%), 308.2 (M^++3, 35%). Anal. Calcd for $C_{16}H_{16}ClNO_3$: C, 62.85; H, 5.27; N, 4.58. Found: C, 62.61; H, 5.33; N, 4.81.

*4.3.15. Ethyl 4-(2-nitrophenyl)-2-methyl-5-methylene-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (**6f**)*

Yield: 69% (0.50 g from 0.75 g) as a white solid, mp 169–171 °C, R_f=0.35 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1637 (CONH), 1702 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.07 (t, 3H, *J*=7.1 Hz, OCH_2CH_3), 2.47 (s, 3H, CH_3), 3.95–4.07 (m, 2H, OCH_2CH_3), 5.67 (d, 1H, *J*=1.0 Hz, CH), 6.09 (s, 1H, =C*H*H), 6.51 (s, 1H, =CH*H*), 7.28–7.40 (m, 2H, ArH), 7.48–7.54 (m, 1H, ArH), 7.78 (dd, 1H, J_1=1.2 Hz, J_2=8.1 Hz, ArH), 8.99 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.0, 19.1, 39.4, 60.5, 107.1, 124.6, 127.7, 129.1, 129.4, 133.4, 137.2, 138.7, 146.1, 148.8, 164.4, 165.8; mass (ES^+) *m/z*=317.1 (M^++1, 86%). Anal. Calcd for $C_{16}H_{16}N_2O_5$: C, 60.75; H, 5.10; N, 8.86. Found: C, 61.05; H, 4.93; N, 9.09.

*4.3.16. Ethyl 4-(2-fluorophenyl)-2-methyl-5-methylene-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (**6g**)*

Yield: 70% (0.70 g from 1.00 g) as a white solid, mp 134–136 °C, R_f=0.45 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1639

(CONH), 1695 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.13 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.44 (s, 3H, CH_3), 4.04 (q, 2H, J=7.1 Hz, OCH_2CH_3), 5.25 (s, 1H, CH), 5.75 (s, 1H, =CHH), 6.34 (s, 1H, =CHH), 6.98–7.04 (m, 2H, ArH), 7.11–7.18 (m, 2H, ArH), 7.68 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.1, 19.1, 39.5, 60.3, 106.0, 115.8, 116.1, 124.4, 127.4, 128.2, 128.6, 128.7, 130.2, 130.4, 138.1, 146.0, 158.7, 161.9, 164.7, 166.3; mass (ES^+) m/z=290.5 (M^++1, 100%). Anal. Calcd for $C_{16}H_{16}FNO_3$: C, 66.43; H, 5.57; N, 4.84. Found: C, 66.54; H, 5.33; N, 4.98.

4.3.17. Ethyl 4-(2,6-dichlorophenyl)-2-methyl-5-methylene-6-oxo-1,4,5,6-tetrahydropyridine-3-carboxylate (**6h**)

Yield: 70% (0.78 g from 1.10 g) as a white solid, mp 193–195 °C, R_f=0.53 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1628 (CONH), 1693 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.02 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.34 (s, 3H, CH_3), 3.96 (q, 2H, J=7.1 Hz, OCH_2CH_3), 5.48 (d, 1H, J=2.6 Hz, CH), 5.83 (d, 1H, J=1.8 Hz, =CHH), 6.50 (d, 1H, J=1.8 Hz, =CHH), 7.09 (t, 1H, J=8.0 Hz, ArH), 7.26 (s, 2H, ArH), 7.86 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.9, 19.4, 41.4, 60.1, 103.7, 127.1, 128.2, 136.4, 141.4, 144.8, 163.3, 166.3; mass (ES^+) m/z=340.2 (M^++1, 100%), 342.2 (M^++3, 70%). Anal. Calcd for $C_{16}H_{15}Cl_2NO_3$: C, 56.49; H, 4.44; N, 4.12. Found: C, 56.35; H, 4.18; N, 3.91.

4.4. General procedure for the preparation of **7a–c** as exemplified for **7a**

Following the general procedure described for **3–4a–f**, acetate **2a** (1.05 g, 5.2 mmol) was reacted with cyclopentanone-2-carboxylate (0.83 mL, 5.32 mmol) in the presence of DABCO (0.87 g, 7.83 mmol) for 2 h. Usual work up followed by purification with hexane/EtOAc (9:1, v/v) yielded 1.29 g (83%) of compound **7a** as colorless oil.

4.4.1. Ethyl 1-(2-cyano-1-phenylallyl)-2-oxocyclopentanecarboxylate (**7a**) (diastereoisomeric mixture, 2.5:1)

R_f=0.50 (hexane/EtOAc, 90:10); ν_{max} (neat) 1721 (CO_2Et), 1753 (CO), 2225 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=0.96 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.29 (t, 3H, J=7.1 Hz, $CO_2CH_2CH_3$), 1.47–1.56 (m, 2H, 2×1H, CH_2), 1.59–1.66 (m, 1H, 1H of CH_2), 1.78–1.92 (m, 1H, 1H of CH_2), 1.99–2.04 (m, 1H, 1H of CH_2), 2.19–2.32 (m, 4H, 2×CH_2), 2.41–2.55 (m, 1H, 1H of CH_2), 2.87–2.95 (m, 2H, 2×1H of CH_2), 3.93 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.21 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.62 (s, 1H, CH), 4.72 (s, 1H, CH), 5.84 (s, 1H, J=0.6 Hz, =CHH), 5.88 (s, 1H, J=1.1 Hz, =CHH), 6.00 (s, 1H, =CHH), 6.06 (s, 1H, =CHH), 7.24–7.33 (m, 2×5H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.7, 14.1, 19.6, 19.8, 27.5, 28.3, 30.0, 38.0, 38.2, 52.7, 52.8, 54.9, 61.4, 62.1, 62.4, 64.8, 65.9, 118.5, 118.8, 123.1, 123.5, 128.1, 128.2, 128.9, 129.3, 130.0, 133.0, 135.6, 135.9, 136.3, 168.5, 212.2, 212.3; mass (ES^+) m/z=298.2 (M^++1, 100%). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.97; H, 6.29; N, 4.44.

4.4.2. Ethyl 1-[2-cyano-1-(4-methylphenyl)allyl]-2-oxocyclopentanecarboxylate (**7b**) (diastereoisomeric mixture, 3:1)

Yield: 78% (1.25 g from 1.10 g) as colorless oil, R_f=0.51 (hexane/EtOAc, 90:10); ν_{max} (neat) 1724 (CO_2Et), 1753 (CO), 2223 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=0.99 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.28 (t, 3H, J=7.1 Hz, $CO_2CH_2CH_3$), 1.55–1.67 (m, 2H, 2×1H of CH_2), 1.82–1.99 (m, 2H, 2×1H of CH_2), 2.24–2.31 (m, 10H, 2×CH_2 and 2×$ArCH_3$), 2.39–2.47 (m, 2H, 2×1H of CH_2), 2.86–2.92 (s, 2H, 2×1H of CH_2), 3.93 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.20 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.57 (s, 1H, CH), 4.68 (s, 1H, CH), 5.85 (s, 1H, =CHH), 5.86 (s, 1H, =CHH), 5.97 (s, 1H, =CHH), 6.04 (s, 1H, =CHH), 7.12–7.18 (m, 8H, 2×4ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.8, 14.1, 19.6, 19.9, 21.1, 27.5, 28.2, 30.0, 38.1, 38.2, 38.3, 52.4, 52.5, 54.9, 62.1, 62.4, 64.8, 65.9, 118.7, 118.9, 123.2, 123.7, 129.2, 129.6, 129.8, 132.7, 132.8, 133.2, 135.4, 137.9, 138.0, 167.9, 168.6, 212.3, 212.5; mass (ES^+) m/z=312.1 (M^++1, 100%). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.33; H, 6.90; N, 4.54.

4.4.3. Ethyl 1-[1-(4-chlorophenyl)-2-cyanoallyl]-2-oxocyclopentanecarboxylate (**7c**) (diastereoisomeric mixture, 2:1)

Yield: 72% (1.25 g from 1.28 g) as colorless oil, R_f=0.49 (hexane/EtOAc, 90:10); ν_{max} (neat) 1724 (CO_2Et), 1735 (CO), 2225 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.01 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.29 (t, 3H, J=7.1 Hz, $CO_2CH_2CH_3$), 1.60–1.68 (m, 4H, 2×2CH_2), 1.86–1.99 (m, 1H, 1H of CH_2), 2.23–2.32 (m, 4H, 2×2CH_2), 2.39–2.52 (m, 1H, 1H of CH_2), 2.87–2.92 (s, 2H, 2×1H of CH_2), 3.94 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.21 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.61 (s, 1H, CH), 4.70 (s, 1H, CH), 5.86 (s, 1H, =CHH), 5.90 (s, 1H, =CHH), 6.01 (s, 1H, =CHH), 6.08 (s, 1H, =CHH), 7.20–7.26 (m, 4H, 2×2ArH), 7.28–7.33 (m, 4H, 2×2ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.8, 14.1, 19.6, 19.8, 21.1, 28.3, 29.8, 37.9, 38.1, 52.0, 52.2, 54.9, 62.3, 62.5, 64.8, 65.8, 118.3, 118.6, 122.6, 123.1, 129.1, 130.6, 131.3, 133.3, 134.2, 134.4, 134.5, 134.9, 135.9, 167.6, 168.2, 211.9; mass (ES^+) m/z=332.2 (M^++1, 55%), 349 (M^++18, 100%). Anal. Calcd for $C_{18}H_{18}ClNO_3$: C, 65.16; H, 5.47; N, 4.22. Found: C, 65.26; H, 5.50; N, 4.15.

4.5. General procedure for the preparation of **8a–c** as exemplified for **8a**

Following the general procedure for **5–6a–f**, compound **7a** (1.25 g, 4.2 mmol) was treated with 7.5 mL of TFA/H_2SO_4 (4:1, v/v) for 7 min. Normal work up followed by purification through column chromatography using benzene/EtOAc (70:30, v/v) as eluent first yielded 0.12 g *trans*-**8a** as a white solid followed by 0.09 g of *cis*-**8a** also as a white solid [a total of 0.64 g (51%) of compound **8a** (both isomers, 0.43 g obtained as mixture of cis and trans) was isolated during column chromatography].

*4.5.1. trans-Ethyl 3-methylene-2-oxo-4-phenyl-1,2,3,4,5,6-hexahydro-4aH-cyclopenta[b]pyridine-4a-carboxylate (**8a**)*

Mp 142–143 °C, R_f=0.47 (benzene/EtOAc, 70:30); ν_{max} (KBr) 1675 (CONH), 1703 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.24 (t, 3H, J=7.0 Hz, OCH_2CH_3), 1.62–1.67 (m, 1H, 1H of CH_2), 2.03–2.07 (m, 2H, 1H of CH_2 merged with 1H of other CH_2), 2.27–2.34 (m, 1H, 1H of CH_2), 4.19 (q, 2H, J=7.0 Hz, OCH_2CH_3), 4.36 (s, 1H, CH), 5.18 (s, 1H, =CH), 5.55 (s, 1H, =C*H*H), 6.40 (d, 1H, J=1.2 Hz, =CH*H*), 7.13 (d, 2H, J=7.2 Hz, ArH), 7.27 (t, 3H, J=7.2 Hz, ArH), 8.85 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.2, 28.9, 31.5, 51.0, 58.6, 61.7, 109.1, 127.4, 127.7, 128.8, 128.9, 129.4, 136.1, 138.0, 139.9, 163.9, 174.4; mass (ES^+) m/z=298.2 (M^++1, 48%). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.40; H, 6.49; N, 4.49.

*4.5.2. cis-Ethyl 3-methylene-2-oxo-4-phenyl-1,2,3,4,5,6-hexahydro-4aH-cyclopenta[b]pyridine-4a-carboxylate (**8a**)*

Mp 176–177 °C, R_f=0.49 (benzene/EtOAc, 70:30); ν_{max} (KBr) 1672 (CONH), 1730 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.22 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.70–1.74 (m, 2H, CH_2), 2.30–2.42 (m, 2H, CH_2), 3.76 (t, 1H, J=2.7 Hz, =CH), 4.15 (q, 2H, J=7.1 Hz, OCH_2CH_3), 5.09 (s, 1H, CH), 5.17 (s, 1H, =C*H*H), 6.50 (d, 1H, J=1.6 Hz, =CH*H*), 7.12–7.15 (m, 2H, ArH), 7.27–7.36 (m, 3H, ArH), 8.65 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.0, 28.6, 34.4, 55.3, 58.6, 61.3, 106.3, 124.3, 127.9, 128.8, 129.4, 130.1, 137.0, 137.7, 139.4, 164.7, 170.7; mass (ES^+) m/z=298.2 (M^++1, 100%). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 73.05; H, 6.58; N, 4.59.

*4.5.3. trans-Ethyl 3-methylene-2-oxo-4-(4-methylphenyl)-1,2,3,4,5,6-hexahydro-4aH-cyclopenta[b]pyridine-4a-carboxylate (**8b**)*

Yield: 47% (0.31 g from 0.65 g, total yield of trans and cis diastereoisomers) as a white solid, mp 96–97 °C, R_f=0.50 (benzene/EtOAc, 70:30); ν_{max} (KBr) 1679 (CONH), 1724 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.24 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.61–1.72 (m, 1H, 1H of CH_2), 1.99–2.12 (m, 2H, 1H of CH_2 merged with 1H of CH_2), 2.31–2.36 (m, 4H, 1H of CH_2 and $ArCH_3$), 4.19 (q, 2H, J=7.2 Hz, OCH_2CH_3), 4.31 (s, 1H, CH), 5.14 (s, 1H, =CH), 5.53 (s, 1H, =C*H*H), 6.37 (d, 1H, J=1.0 Hz, =CH*H*), 7.00 (d, 2H, J=8.0 Hz, ArH), 7.11 (d, 2H, J=8.0 Hz, ArH), 8.27 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.3, 21.1, 28.9, 31.5, 31.7, 50.7, 58.7, 61.7, 108.9, 127.5, 128.7, 129.6, 136.3, 136.8, 137.1, 138.3, 163.9, 174.5; mass (ES^+) m/z=312.1 (M^++1, 100%). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.55; H, 6.98; N, 4.29.

*4.5.4. cis-Ethyl 3-methylene-2-oxo-4-(4-methylphenyl)-1,2,3,4,5,6-hexahydro-4aH-cyclopenta[b]pyridine-4a-carboxylate (**8b**)*

Yield: 47% (0.31 g from 0.65 g, total yield of trans and cis diastereoisomers) as a white solid, mp 106–107 °C, R_f=0.48 (benzene/EtOAc, 70:30); ν_{max} (KBr) 1680 (CONH), 1732 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.23 (t, 3H, J=7.2 Hz, OCH_2CH_3), 1.68–1.77 (m, 2H, CH_2), 2.29–2.42 (m, 5H, 2H of CH_2 merged with 3H of $ArCH_3$), 3.72 (t, 1H, J=2.7 Hz, CH), 4.14 (q, 2H, J=7.2 Hz, OCH_2CH_3), 5.06 (s, 1H, =CH), 5.18 (s, 1H, =C*H*H), 6.49 (d, 1H, J=1.5 Hz, =CH*H*), 7.01 (d, 2H, J=8.1 Hz, ArH), 7.14 (d, 2H, J=8.1 Hz, ArH), 8.32 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=11.4, 18.6, 26.0, 56.0, 56.2, 58.8, 104.0, 121.8, 124.8, 125.9, 126.7, 127.0, 127.5, 131.2, 131.7, 135.0, 136.5, 136.9, 170.0; mass (ES^+) m/z=312.3 (M^++1, 100%). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.55; H, 6.98; N, 4.29.

*4.5.5. trans-Ethyl 4-(4-chlorophenyl)-3-methylene-2-oxo-1,2,3,4,5,6-hexahydro-4aH-cyclopenta[b]pyridine-4a-carboxylate (**8c**)*

Yield: 53% (0.53 g from 1.0 g, total yield of trans and cis diastereoisomers) as colorless oil, R_f=0.50 (benzene/EtOAc, 70:30); ν_{max} (KBr) 1634 (CONH), 1722 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.23 (t, 3H, J=7.0 Hz, $O_2CH_2CH_3$), 1.56–1.66 (m, 1H, 1H of CH_2), 2.03–2.13 (m, 2H, 1H of CH_2 merged with 1H of CH_2), 2.28–2.39 (s, 1H, 1H of CH_2), 4.19 (q, 2H, J=7.0 Hz, OCH_2CH_3), 4.35 (s, 1H, CH), 5.15 (t, 1H, J=2.4 Hz, =CH), 5.54 (s, 1H, =C*H*H), 6.40 (d, 1H, J=1.2 Hz, =CH*H*), 7.06 (d, 2H, J=8.5 Hz, ArH), 7.26 (d, 2H, J=8.5 Hz, ArH), 8.06 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.2, 28.9, 31.4, 50.3, 53.5, 58.5, 61.8, 109.7, 128.1, 129.1, 129.3, 130.1, 130.8, 133.3, 135.8, 137.7, 138.4, 163.8, 174.1; mass (ES^+) m/z=332.1 (M^++1, 100%). Anal. Calcd for $C_{18}H_{18}ClNO_3$: C, 65.16; H, 5.47; N, 4.22. Found: C, 64.88; H, 5.44; N, 4.39.

*4.5.6. cis-Ethyl 4-(4-chlorophenyl)-3-methylene-2-oxo-1,2,3,4,5,6-hexahydro-4aH-cyclopenta[b]pyridine-4a-carboxylate (**8c**)*

Yield: 53% (0.53 g from 1.0 g, total yield of trans and cis diastereoisomers) as colorless oil, R_f=0.48 (benzene/EtOAc, 70:30); ν_{max} (neat) 1670 (CONH), 1734 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ=1.24 (t, 3H, J=7.2 Hz, $CO_2CH_2CH_3$), 1.68–1.72 (m, 1H, CH_2), 2.30–2.43 (m, 3H, 1H of CH_2 merged with CH_2), 3.76 (t, 1H, J=2.7 Hz, =CH), 4.10–4.18 (m, 3H, 2H of OCH_2CH_3), 5.14 (s, 1H, =CH_2), 6.52 (s, 1H, =CH_2), 7.10 (d, 2H, J=8.4 Hz, ArH), 7.33 (d, 2H, J=8.4 Hz, ArH), 8.95 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.0, 29.6, 34.3, 54.7, 58.5, 61.4, 106.4, 124.1, 129.0, 130.8, 133.8, 135.6, 140.5, 139.2, 164.4, 170.5; mass (ES^+) m/z=332.0 (M^++1, 100%), 334.0 (M^++3, 30%). Anal. Calcd for $C_{18}H_{18}ClNO_3$: C, 65.16; H, 5.47; N, 4.22. Found: C, 65.29; H, 5.57; N, 4.11.

*4.6. General procedure for the preparation of compounds **9–12b**, **13–17c**, **18–21f** as exemplified for **18f***

To a stirred solution of **6f** (0.2 g, 0.63 mmol) and benzene hydroximoyl chloride (0.147 g, 0.95 mmol) in anhydrous diethylether (15 mL) was added dropwise a solution of Et_3N (0.13 mL, 0.95 mmol) at −78 °C under stirring. After the addition was complete the reaction was allowed to stir at

room temperature. After 6 h of stirring the reaction was quenched with water (60 mL) and the resulting mixture was partitioned in a separating funnel. The aqueous layer was separated and further extracted with EtOAc (2×20 mL). The organic layers were pooled, washed with brine (45 mL), dried over anhydrous Na_2SO_4, and concentrated to afford a residue which was purified via silica gel column chromatography. Elution with hexane/EtOAc (9:1, v/v) furnished 0.28 g (89%) of **18f** as a white solid.

*4.6.1. 9-Acetyl-8-methyl-10-(4-methylphenyl)-3-phenyl-1-oxa-2,7-diazaspiro[4.5]deca-2,8-dien-6-one (**9b**)*

Yield: 82% (0.27 g from 0.23 g) as a white solid, mp 160–162 °C, R_f=0.28 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1680 (CONH), 1720 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.15 (s, 3H, $ArCH_3$), 2.33 (s, 3H, CH_3), 2.43 (s, 3H, $COCH_3$), 3.15 (d, 1H, J=17.2 Hz, C*H*H), 3.80 (d, 1H, J=17.2 Hz, CH*H*), 4.17 (s, 1H, CH), 7.06 (d, 2H, J=8.0 Hz, ArH), 7.14 (d, 2H, J=8.0 Hz, ArH), 7.39 (d, 3H, J=7.1 Hz, ArH), 7.59 (s, 1H, NH), 7.62–7.67 (m, 2H, ArH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=20.3, 21.5, 30.5, 38.6, 50.4, 87.2, 117.0, 127.4, 128.7, 129.2, 130.6, 130.9, 133.9, 138.6, 143.9, 157.7, 167.0, 197.6; mass (ES^+) m/z=375.0 (M^++1, 100%). Anal. Calcd for $C_{23}H_{22}N_2O_3$: C, 73.78; H, 5.92; N, 7.48. Found: C, 73.61; H, 6.16; N, 7.28.

*4.6.2. 9-Acetyl-8-methyl-3,10-di(4-methylphenyl)-1-oxa-2,7-diazaspiro[4.5]deca-2,8-dien-6-one (**10b**)*

Yield: 83% (0.38 g from 0.3 g) as a white solid, mp 187–189 °C, R_f=0.32 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1636 (CONH), 1700 ($COCH_3$) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.14 (s, 3H, $ArCH_3$), 2.33 (s, 3H, CH_3), 2.37 (s, 3H, $ArCH_3$), 2.43 (s, 3H, $COCH_3$), 3.13 (d, 1H, J=17.2 Hz, C*H*H), 3.78 (d, 1H, J=17.2 Hz, CH*H*), 4.16 (s, 1H, CH), 7.06 (d, 2H, J=8.1 Hz, ArH), 7.14 (d, 2H, J=8.0 Hz, ArH), 7.19 (d, 2H, J=8.0 Hz, ArH), 7.53 (br d, 3H, J=8.1 Hz, 1H of NH merged with ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=20.0, 21.2, 21.6, 30.2, 38.4, 50.1, 86.7, 116.7, 126.0, 127.0, 128.4, 129.5, 130.3, 133.6, 138.2, 141.0, 143.7, 157.3, 166.8, 197.4; mass (FAB^+) m/z=389 (M^++1, 100%). Anal. Calcd for $C_{24}H_{24}N_2O_3$: C, 74.21; H, 6.23; N, 7.21. Found: C, 74.48; H, 6.39; N, 7.50.

*4.6.3. 9-Acetyl-3-(4-chlorophenyl)-8-methyl-10-(4-methylphenyl)-1-oxa-2,7-diazaspiro[4.5]deca-2,8-dien-6-one (**11b**)*

Yield: 85% (0.82 g from 0.6 g) as a white solid, mp 233–235 °C, R_f=0.34 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1643 (CONH), 1700 ($COCH_3$) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=2.16 (s, 3H, $ArCH_3$), 2.33 (s, 3H, CH_3), 2.43 (s, 3H, $COCH_3$), 3.12 (d, 1H, J=17.2 Hz, C*H*H), 3.76 (d, 1H, J=17.2 Hz, CH*H*), 4.18 (s, 1H, CH), 7.06 (d, 2H, J=8.0 Hz, ArH), 7.14 (d, 2H, J=8.0 Hz, ArH), 7.34–7.41 (m, 2H, ArH), 7.53–7.64 (m, 3H, NH merged with ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=18.2, 20.0, 29.2, 36.8, 48.4, 86.1, 114.8, 126.5, 127.2, 127.3, 128.0, 129.0, 133.0, 135.0, 136.7, 144.4, 152.3, 165.2, 196.1; mass (ES^+) m/z=409.1 (M^++1, 100%), 411.1 (M^++3, 35%). Anal. Calcd for $C_{23}H_{21}ClN_2O_3$: C, 67.56; H, 5.18; N, 6.85. Found: C, 67.35; H, 5.30; N, 6.77.

*4.6.4. Ethyl 9-acetyl-8-methyl-6-oxo-10-(4-methylphenyl)-1-oxa-2,7-diazaspiro[4.5]deca-2,8-diene-3-carboxylate (**12b**)*

Yield: 87% (0.38 g from 0.3 g) as a white solid, mp 138–140 °C, R_f=0.25 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1683 (CONH), 1724 ($COCH_3$) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.36 (s, 3H, J=7.1 Hz, OCH_2CH_3), 2.14 (s, 3H, $ArCH_3$), 2.32 (s, 3H, CH_3), 2.43 (s, 3H, $COCH_3$), 3.04 (d, 1H, J=18.4 Hz, C*H*H), 3.65 (d, 1H, J=18.4 Hz, CH*H*), 4.12 (s, 1H, CH), 4.35 (q, 3H, J=7.1 Hz, OCH_2CH_3), 7.03 (d, 2H, J=8.0 Hz, ArH), 7.13 (d, 2H, J=8.0 Hz, ArH), 7.53 (d, 2H, J=8.6 Hz, ArH), 7.58 (s, 1H, NH), 7.62 (d, 2H, J=8.6 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.2, 20.0, 21.1, 30.2, 37.0, 49.8, 62.5, 89.3, 116.5, 128.3, 130.4, 132.6, 138.5, 143.4, 152.2, 160.0, 165.5, 197.1; mass (ES^+) m/z=371.1 (M^++1, 100%). Anal. Calcd for $C_{20}H_{22}N_2O_5$: C, 64.85; H, 5.99; N, 7.56. Found: C, 65.06; H, 6.20; N, 7.60.

*4.6.5. Ethyl 10-(4-chlorophenyl)-8-methyl-6-oxo-3-phenyl-1-oxa-2,7-diazaspiro[4.5]deca-2,8-diene-9-carboxylate (**13c**)*

Yield: 86% (0.42 g from 0.35 g) as a white solid, mp 105–107 °C, R_f=0.50 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1640 (CONH), 1708 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.21 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.47 (s, 3H, CH_3), 2.96 (d, 1H, J=17.1 Hz, C*H*H), 3.80 (d, 1H, J=17.1 Hz, CH*H*), 4.10 (q, 3H, J=7.1 Hz, OCH_2CH_3), 4.32 (s, 1H, CH), 7.12 (d, 2H, J=8.5 Hz, ArH), 7.27–7.30 (m, 3H, ArH), 7.35 (d, 2H, J=8.5 Hz, ArH), 7.41 (s, 1H, NH), 7.55 (d, 2H, J=8.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.2, 19.3, 38.6, 49.1, 60.6, 86.4, 108.2, 127.1, 127.7, 128.8, 128.9, 129.0, 129.5, 129.8, 130.2, 130.7, 134.0, 136.6, 144.6, 157.2, 166.1, 166.7; mass (FAB^+) m/z=425 (M^++1, 100%). Anal. Calcd for $C_{23}H_{21}ClN_2O_4$: C, 65.02; H, 4.98; N, 6.59. Found: C, 64.84; H, 5.01; N, 6.66.

*4.6.6. Ethyl 10-(4-chlorophenyl)-8-methyl-3-(4-methylphenyl)-6-oxo-1-oxa-2,7-diazaspiro[4.5]deca-2,8-diene-9-carboxylate (**14c**)*

Yield: 86% (0.23 g from 0.2 g) as a white solid, mp 177–179 °C, R_f=0.50 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1680 (CONH), 1705 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.20 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.37 (s, 3H, $ArCH_3$), 2.46 (s, 3H, CH_3), 2.98 (d, 1H, J=17.1 Hz, C*H*H), 3.82 (d, 1H, J=17.1 Hz, CH*H*), 4.09 (q, 3H, J=7.1 Hz, OCH_2CH_3), 4.31 (s, 1H, CH), 7.12 (d, 2H, J=8.4 Hz, ArH), 7.18 (d, 2H, J=8.1 Hz, ArH), 7.28 (d, 2H, J=8.4 Hz, ArH), 7.52 (d, 2H, J=8.1 Hz, ArH), 7.57 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.2, 19.3, 21.6, 38.7, 49.1, 60.6, 86.2, 108.1, 125.9, 127.0, 129.5, 129.6, 129.8, 133.9, 136.6, 141.0, 144.7, 157.2, 166.1, 166.9; mass (FAB^+) m/z=439 (M^++1, 20%). Anal. Calcd for $C_{24}H_{23}ClN_2O_4$: C, 65.68; H, 5.28; N, 6.38. Found: C, 65.88; H, 5.09; N, 6.55.

*4.6.7. Ethyl 3,10-di(4-chlorophenyl)-8-methyl-6-oxo-1-oxa-2,7-diazaspiro[4.5]deca-2,8-diene-9-carboxylate (**15c**)*

Yield: 87% (0.46 g from 0.35 g) as a white solid, mp 178–180 °C, R_f=0.52 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1677 (CONH), 1706 (CO_2Et) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.20 (t, 3H, J=7.2 Hz, OCH_2CH_3), 2.44 (s, 3H, CH_3), 2.98 (d, 1H, J=17.1 Hz, C*H*H), 3.80 (d, 1H, J=17.1 Hz, CH*H*), 4.09 (q, 3H, J=7.1 Hz, OCH_2CH_3), 4.33 (s, 1H, CH), 7.13 (d, 2H, J=8.6 Hz, ArH), 7.29 (d, 2H, J=8.6 Hz, ArH), 7.36 (d, 2H, J=8.6 Hz, ArH), 7.56 (d, 2H, J=8.6 Hz, ArH), 8.42 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=14.5, 19.6, 38.7, 49.3, 60.9, 86.9, 108.4, 127.5, 128.6, 129.5, 129.8, 130.0, 134.3, 136.7, 137.0, 144.9, 156.6, 166.3, 167.0; mass (FAB^+) m/z=459.0 (M^++1, 82%), 461 (M^++3, 52%). Anal. Calcd for $C_{23}H_{20}Cl_2N_2O_4$: C, 60.14; H, 4.39; N, 6.10. Found: C, 59.91; H, 4.59; N, 6.06.

*4.6.8. Diethyl 10-(4-chlorophenyl)-8-methyl-6-oxo-1-oxa-2,7-diazaspiro[4.5]deca-2,8-diene-3,9-dicarboxylate (**16c**)*

Yield: 91% (0.29 g from 0.23 g) as a white solid, mp 101–103 °C, R_f=0.48 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1641 (CONH), 1716 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.21 (t, 3H, J=7.1 Hz, OCH_2CH_3), 1.35 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.47 (s, 3H, CH_3), 2.89 (d, 1H, J=18.2 Hz, C*H*H), 3.69 (d, 1H, J=18.2 Hz, CH*H*), 4.01 (q, 3H, J=7.1 Hz, OCH_2CH_3), 4.28 (s, 1H, CH), 4.34 (q, 3H, J=7.1 Hz, OCH_2CH_3), 7.07 (d, 2H, J=8.5 Hz, ArH), 7.27 (d, 2H, J=8.5 Hz, ArH), 7.47 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.2, 19.3, 22.7, 31.7, 37.3, 48.8, 60.7, 62.5, 88.8, 108.0, 129.6, 129.7, 134.2, 135.6, 144.5, 152.0, 160.0, 165.6, 165.9; mass (FAB^+) m/z=421 (M^++1, 100%). Anal. Calcd for $C_{20}H_{21}ClN_2O_6$: C, 57.08; H, 5.03; N, 6.66. Found: C, 57.31; H, 5.16; N, 6.79.

*4.6.9. Ethyl 3-(2-chlorophenyl)-10-(4-chlorophenyl)-8-methyl-6-oxo-1-oxa-2,7-diazaspiro[4.5]deca-2,8-diene-9-carboxylate (**17c**)*

Yield: 91% (0.14 g from 0.1 g) as a white solid, mp 148–150 °C, R_f=0.51 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1638 (CONH), 1704 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.22 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.48 (s, 3H, CH_3), 3.25 (d, 1H, J=17.6 Hz, C*H*H), 3.89 (d, 1H, J=17.6 Hz, CH*H*), 4.11 (q, 2H, J=7.1 Hz, OCH_2CH_3), 4.37 (s, 1H, CH), 7.13 (d, 2H, J=8.5 Hz, ArH), 7.27 (d, 3H, J=8.6 Hz, ArH), 7.31–7.44 (m, 3H, ArH), 7.51 (s, 1H, NH), 7.59 (dd, 1H, J_1=1.8 Hz, J_2=7.4 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.3, 19.2, 40.8, 48.9, 60.6, 86.9, 108.1, 127.2, 128.1, 129.5, 129.7, 130.7, 131.0, 131.4, 133.0, 136.3, 144.6, 157.2, 166.1, 166.6; mass (ES^+) m/z=459.0 (M^++1, 70%), 461.0 (M^++3, 50%). Anal. Calcd for $C_{23}H_{20}Cl_2N_2O_4$: C, 60.14; H, 4.39; N, 6.10. Found: C, 60.30; H, 4.55; N, 5.95.

*4.6.10. Ethyl 8-methyl-10-(2-nitrophenyl)-6-oxo-3-phenyl-1-oxa-2,7-diazaspiro[4.5]deca-2,8-diene-9-carboxylate (**18f**)*

Mp 236–237 °C, R_f=0.25 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1644 (CONH), 1704 (CO_2Et) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.09 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.49 (s, 3H, CH_3), 3.33 (d, 1H, J=16.7 Hz, C*H*H), 3.91–4.10 (m, 3H, CH*H* merged with OCH_2CH_3), 5.10 (s, 1H, CH), 7.31–7.48 (m, 4H, ArH), 7.63–7.67 (m, 3H, NH merged with ArH), 7.79–7.83 (m, 1H, ArH), 7.63–7.67 (m, 2H, ArH), 7.72–7.75 (m, 1H, ArH), 7.88 (s, 1H, NH); ^{13}C NMR (50 MHz, $CDCl_3$) δ=14.3, 19.5, 39.1, 43.1, 61.0, 86.5, 108.2, 125.1, 127.5, 128.8, 129.0, 129.1, 130.9, 133.5, 134.2, 146.2, 150.7, 158.1, 165.9, 166.9; mass (ES^+) m/z=436.0 (M^++1, 35%). Anal. Calcd for $C_{23}H_{21}N_3O_6$: C, 63.44; H, 4.86; N, 9.65. Found: C, 63.12; H, 4.98; N, 9.76.

*4.6.11. Ethyl 8-methyl-3-(4-methylphenyl)-10-(2-nitrophenyl)-6-oxo-1-oxa-2,7-diazaspiro[4.5]deca-2,8-diene-9-carboxylate (**19f**)*

Yield: 87% (0.25 g from 0.2 g) as a white solid, mp 165–167 °C, R_f=0.26 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1640 (CONH), 1709 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.08 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.37 (s, 3H, CH_3), 2.49 (s, 3H, $ArCH_3$), 3.30 (d, 1H, J=16.7 Hz, CH_2), 3.92–4.04 (m, 3H, OCH_2CH_3 and C*H*H), 5.09 (s, 1H, CH), 7.18 (d, 2H, J=8.0 Hz, ArH), 7.26–7.30 (m, 2H, ArH), 7.41–7.47 (m, 1H, ArH), 7.52–7.57 (m, 2H, ArH), 7.64 (s, 1H, NH), 7.79–7.82 (m, 1H, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.8, 19.0, 21.4, 38.7, 42.6, 60.6, 85.9, 107.7, 124.6, 125.7, 127.0, 128.3, 128.8, 129.4, 133.1, 133.7, 140.8, 145.9, 150.3, 157.6, 165.5, 166.6; mass (ES^+) m/z=450.0 (M^++1, 100%). Anal. Calcd for $C_{24}H_{23}N_3O_6$: C, 64.13; H, 5.16; N, 9.35. Found: C, 64.10; H, 5.30; N, 9.52.

*4.6.12. Ethyl 3-(4-chlorophenyl)-8-methyl-10-(2-nitrophenyl)-6-oxo-1-oxa-2,7-diazaspiro[4.5]deca-2,8-diene-9-carboxylate (**20f**)*

Yield: 92% (0.31 g from 0.2 g) as a white solid, mp 121–123 °C, R_f=0.24 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1639 (CONH), 1704 (CO_2Et) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ=1.09 (t, 3H, J=7.1 Hz, OCH_2CH_3), 2.49 (s, 3H, CH_3), 3.29 (d, 1H, J=16.7 Hz, C*H*H), 3.91–4.14 (m, 3H, OCH_2CH_3 and CH*H*), 5.07 (s, 1H, CH), 7.27–7.45 (m, 4H, ArH), 7.49–7.61 (m, 3H, ArH), 7.82 (d, 1H, J=7.9 Hz, ArH), 7.96 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=14.0, 19.2, 38.6, 42.8, 60.8, 86.5, 107.9, 124.8, 127.2, 128.4, 129.0, 129.1, 133.0, 136.7, 145.9, 150.4, 156.9, 165.5, 166.4; mass (ES^+) m/z=470.0 (M^++1, 100%), 472.0 (M^++3, 34%). Anal. Calcd for $C_{23}H_{20}ClN_3O_6$: C, 58.79; H, 4.29; N, 8.94. Found: C, 58.88; H, 4.22; N, 9.06.

*4.6.13. Diethyl 8-methyl-10-(2-nitrophenyl)-6-oxo-1-oxa-2,7-diazaspiro[4.5]deca-2,8-diene-3,9-dicarboxylate (**21f**)*

Yield: 93% (0.25 g from 0.2 g) as a white solid, mp 163–164 °C, R_f=0.25 (hexane/EtOAc, 70:30); ν_{max} (KBr) 1641 (CONH), 1716 (CO_2Et) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ=1.09 (t, 3H, J=7.1 Hz, $CH{=}CO_2CH_2CH_3$), 1.37 (t, 3H, J=7.1 Hz, $N{=}CO_2CH_2CH_3$), 2.50 (s, 3H, CH_3), 3.18 (d, 1H, J=17.8 Hz, C*H*H), 3.82 (d, 1H, J=17.8 Hz, CH*H*), 4.01 (q, 2H, J=7.1 Hz, $CO_2CH_2CH_3$), 4.37 (q, 2H, J=7.1 Hz, $CO_2CH_2CH_3$), 5.06 (s, 1H, CH), 7.20–7.27 (m, 1H, ArH), 7.42–7.47 (m, 1H, ArH), 7.51–7.56 (m, 1H, ArH), 7.82–

7.85 (m, 1H, ArH), 7.91 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$) δ=13.8, 14.0, 19.0, 37.5, 42.5, 60.7, 62.4, 88.3, 107.4, 124.8, 128.2, 129.0, 132.3, 133.8, 145.7, 150.2, 152.3, 159.7, 165.2; mass (ES^+) m/z=432.0 (M^++1, 100%). Anal. Calcd for $C_{20}H_{21}N_3O_8$: C, 55.68; H, 4.91; N, 9.74. Found: C, 55.85; H, 5.13; N, 9.55.

Acknowledgements

Two of the authors (V.S. and G.P.Y.) acknowledge the financial support CSIR, New Delhi in the form of fellowship. This work was supported by a grant from DST, New Delhi.

Supplementary data

Spectroscopic data of all compounds are provided. ^{1}H NMR, ^{13}C NMR, and mass spectra of several new compounds have been included. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.01.074.

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12. Crystal data of compound **21f** (crystallized from $CHCl_3$): $C_{20}H_{21}N_3O_8$, M=431.40, triclinic, P-1, a=12.626 (28.200(1)), b=10.234(1), c=13.433(2) Å, α=103.11(1), β=105.14(1), γ=94.99(1), V=1046.9(2) Å^3, Z=2, D_c=1.369 g cm^{-3}, μ(Mo Kα)=0.107 mm^{-1}, F(000)=452, colorless block, dimension 0.25×0.225×0.175 mm, 4475 reflections measured (R_{int}=0.0234), 3645 unique, $wR2$=0.1454, conventional R=0.0520 on F^2 values of 2616 reflections with $I>2\sigma(I)$, $(\Delta/\sigma)_{max}$=000, S=1.022 for all data and 284 parameters. Unit cell determination and intensity data collection (2θ=50°) were performed on a Bruker P4 diffractometer at 293(2) K. Structure solutions by direct methods and refinements by full-matrix least-squares methods on F^2. Programs: XSCANS (Siemens Analytical X-ray Instrument Inc.: Madison, WI, USA, 1996) for data collection and data processing; SHELXTL-NT (Bruker AXS Inc.: Madison, Wisconsin, USA, 1997) for structure determination, refinements, and molecular graphics. Further details of the crystal structure investigation can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK (CCDC deposition no. 670413).