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Sequential transformations with isoxazol-5-ones: one-pot synthesis of spirotetrahydropyridine-3-carboxylate derivatives

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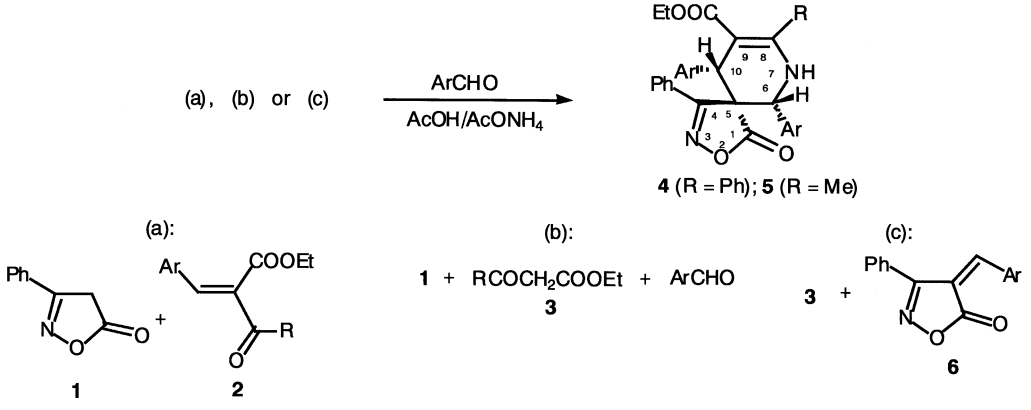
Abstract—Spirotetrahydropyridine-3-carboxylates **4** and **5** were prepared from olefins **2** and isoxazol-5-one **1** through a highly diastereoselective tandem sequential process. Three reaction workup procedures were employed, each of which afforded a different product distribution.

1. Introduction

Spiro heterocycles possess diverse biological properties ranging from central nervous system activity to anti-tumor and anti-fungal effects.[1] Thus, an increasing interest in this class of compounds has led to the development of new synthetic strategies. The tandem (4+2)/(3+2) cycloaddition sequence[2] or radical cyclization[3] have proved extremely versatile means of constructing a diverse array of highly functionalised spiroheterocycle derivatives. In our studies in this area, we recently found a means of improving the chances of achieving (4,4) spiroazoline synthesis using acid-promoted tandem reactions starting from isoxazol-5-ones and selected acyclic compounds.[4] Previously, similar spirans could only be obtained by dipolar 1,3-cycloaddition reactions of 4-arylmethyleneisoxazol-5-one derivatives.[5] Following our results on the application of the aforementioned successful strategy, we now describe the synthesis of unusual spiro(4,5)isoxazolinonetetrahydropyridines which, because they are susceptible to isoxazol-5-one ring opening,[6] would seem to have considerable potential both as synthetic intermediates[7] and in terms of their possible biopharmacological activity.[8]

2. Results and discussion

Thus isoxazol-5-one **1** was treated (a) (Scheme 1) with olefin **2** in the presence of an $AcOH/AcONH_4$ mixture and the appropriate arylaldehyde in refluxing ethanol affording good yields (Table 1) of the spirocompounds **4** and **5**. Useful variations on this procedure can be achieved: (b) by generating olefin **2** in situ starting from dicarbonyl **3** and aldehyde; or (c) by first preparing arylidene **6** and subsequently adding **3**.



Scheme 1.

Keywords: isoxazol-5-ones; spiro compounds; diastereoselection; tandem reactions.
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Table 1. Results of the three synthetic procedures

Ar		Compounds **4**				Compounds **5**				Compounds **11**			
		Mp (°C)	Yield (%)			Mp (°C)	Yield (%)			Mp (°C)	Yield (%)		
			(a)	(b)	(c)		(a)	(b)	(c)		(a)	(b)	(c)
Ph	**a**	190	77	69	71	199	77	61	83		–	–	–
oMeC$_6$H$_4$	**b**	194	–	–	76		–	–	–	117	–	–	81
mMeC$_6$H$_4$	**c**	171	71	63	74	197	49	38	55	127	18	11	20
pMeC$_6$H$_4$	**d**	196	86	66	79	194	70	64	80		–	–	–
oMeOC$_6$H$_4$	**e**	189	–	–	90		–	–	–	157	–	–	82
mMeOC$_6$H$_4$	**f**	187	80	67	84	195	46	41	51	143	12	9	16
pClC$_6$H$_4$	**g**	176	76	58	68		–	–	–		–	–	–

The latter procedure proves particularly efficient with *meta*- and *ortho*-substituted arylaldehydes. This synthetic protocol cannot be extended to aliphatic aldehydes since use of these derivatives produces resinous products and no compounds of interest were ever isolated.

When R=Me spirans **11** were isolated besides **5**. The relative product distribution is most likely determined by competing nucleophilic addition pathways. The reaction seems to proceed through a tandem process involving first Michael addition of **1** to the starting olefin **2** or, alternatively, of **3** to the in situ formed or preformed arylidene derivative **6** to give the intermediate **7**. This evolves to the enamine **8A** or **8B** which undergoes nucleophilic addition to give **9** (Path (i)) or **10** (Path (ii)), and subsequent ring closure[9] to furnish **4** and **5** or **11**, respectively, as represented in Scheme 2.

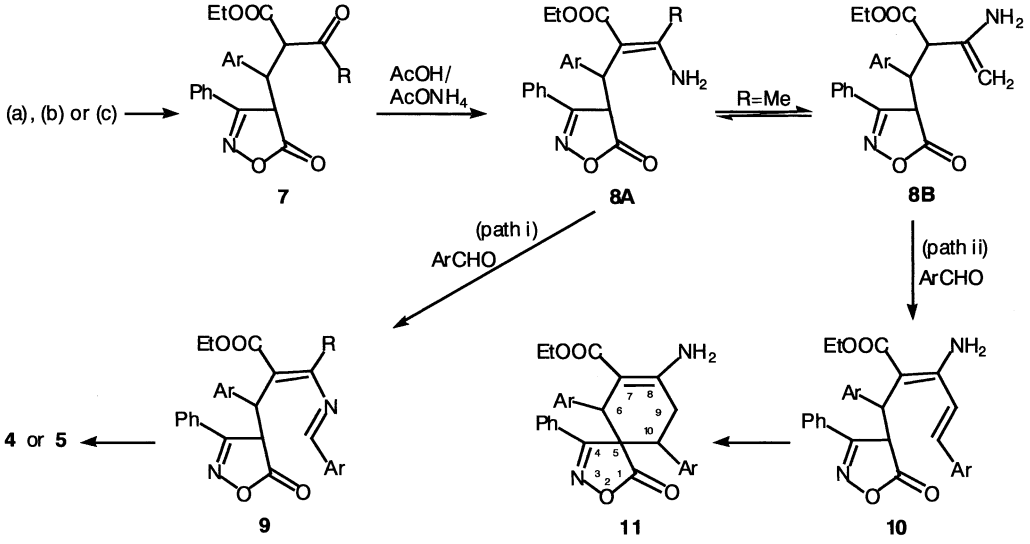
In order to test this hypothesis, the known intermediate **7a**[10] was subjected to the same cyclization conditions (PhCHO, AcOH/AcONH$_4$): **4a** was isolated as the only product in the same yields.

All the spirans **4**, **5** and **11** were fully characterized using analytical and spectroscopic data (Table 1).

The spirotetrahydropyridines **4** and **5** all show the characteristic IR bands for the stetching vibrations of C=O (4,4 disubstituted isoxazol-5-one),[11] C=O (extensively conjugated) and NH around ν=1780 and 1680, 3350 cm^{-1}, respectively; while the spiroderivatives **11** show typical NH$_2$ bands around ν=3300 and 3400 cm^{-1} besides the afore-mentioned carbonyl absorptions. ^{1}H NMR spectra revealed the presence of the OC$_2$H$_5$ group of the original ester function, though at higher fields than expected. In cases **4** and **5** this difference is probably due to interaction with the substituent on the adjacent C$_{sp^2}$ atom, while for **11**, these values return almost to normal since this interaction is reduced. Moreover, the methylene protons in the OC$_2$H$_5$ group for **4** and **5** are anisochronous and resonate like two quartets centred at δ=3.52–3.80 and 3.75–3.89.

Only the enamine form of **4** and **5**, and not the tautomeric imine form, exists in CDCl$_3$ solution and indeed, in all cases studied three singlets were always observed due to H–C(6), H–C(10) and H–N(7), centred at δ=5.45–5.08, 5.12–4.77 and 4.70–4.43, respectively. The last easily exchanges with D$_2$O.

As regards the stereochemical outcome, despite the formation of three new chiral centres, these reactions generally produced a single diastereomer of **4** and **5**; it is thus possible to hypothesize a diastereoselective sequence both in the *C*-alkylation at the 4-position of the isoxazolonic ring and in the subsequent 6-*exo*-trig cyclization.[9]



Scheme 2.

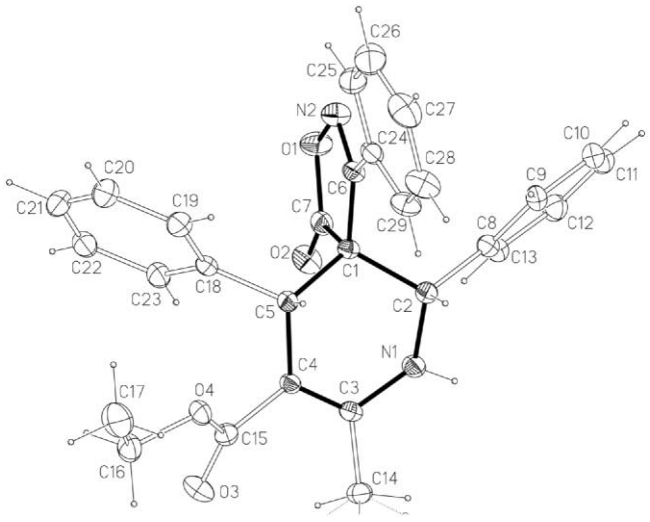


Figure 1. Perspective view and atom numbering scheme of molecule **5a**. Thermal ellipsoids are drawn at 15% of probability, while H size is arbitrary. Selected bond lengths (Å) and angles (°): C3–C4 1.344(3), C4–C15 1.465(3), C2–N1 1.452(3), C6–N2 1.290(3), C6–C24 1.472(4), N2–O1 1.431(3), O1–C7 1.371(3), C7–O2 1.191(3), C3–C4–C15 120.4(3), C4–C3–C14 125.8(3), C24–C6–C1 129.7(3), C3–C4–C15–O3 −34.3(5), C1–C6–C24–C29 16.8(5).

Since the above spectroscopic data seemed insufficient for the purposes of definitive stereochemical characterization, in the case of compounds **4** unequivocal attribution of configuration was possible by 2D-NOESY NMR experiments. Thus, irradiation of H-6 resulted in NOE enhancement for H-10 and the *ortho*-protons of the phenyl at C-4, indicating a *cis*-spatial relationship between these protons and the Ph on C-4.

Finally, the stereostructural features of spiroderivatives were unambigously confirmed by a X-ray analysis carried out on a compound **5**, namely **5a** (Fig. 1). In the solid state, **5a** is a racemic mixture due to the crystallographic centrosymmetric space group (the picture shows the enantiomer *S*, *S*, *S* for the chiral carbon atoms C1, C2 and C5, respectively). The flat conformation of the isoxazolone ring conjugated with the phenyl substituent has been already observed in other analogous compounds[12] showing comparable geometric values. The tetrahydropyridine ring adopts the half-chair conformation with the carbon C1 deviating 0.616(3) Å from the mean plane passing through the other five atoms. In the crystal packing the nitrogen N1 shows a significant hydrogen interaction with the ester group of the adjacent molecule at $0.5+x$, $0.5-y$, $0.5+z$ [N1H···O3 2.26(3) Å and N1–H···O3 168(2)°].

In the light of these results, spirotetrahydropyridine-3-carboxylates **4** and **5** appear in the same configurations (C-5S*, C-6S*, C-10S*) (Scheme 1).

3. Experimental

3.1. General

Melting points were determined using Reichert–Kofler apparatus and are uncorrected. IR spectra were performed using Nicolet FT-IR Impact 400D spectrometer and microanalyses using a Carlo Erba 1102 element analyser. ^{1}H and ^{13}C NMR were recorded on a Bruker ARX 300 spectrometer, in the solvent indicated. Chemical shifts (δ) are given relative to TMS, which was used as an internal reference. All solvents and reagents were obtained from commercial sources and purified before use if necessary. Compounds **1**[6], **2**[13] and **6**[14] were prepared according to the literature methods.

3.2. Preparation of compounds 4, 5 and 11

3.2.1. Procedure (a). To a stirred solution of isoxazol-5-one **1** (1.6 g, 10 mmol), olefin **2** (12 mmol) and $AcONH_4$ (3.85 g, 50 mmol) in EtOH (80 mL), containing suspended molecular sieves 4 Å, the appropriate arylaldehyde (10 mmol) and glacial AcOH (2 mL) were added and the reaction mixture refluxed for 1 h. The solvent was evaporated and the residue extracted with benzene (4×8 mL). The combined extracts were filtered and evaporated to give an oily residue which was crystallized from methanol to afford **4**, **5** and/or **11** as white solids (Table 1).

4a: [Found: C, 77.55; H, 5.49; N, 5.49. $C_{34}H_{28}N_2O_4$ requires C, 77.25; H, 5.34; N, 5.30%]; ν_{max} (Nujol) 1680, 1798, 3347 cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 0.54 (3H, t, J=7.1 Hz, *Me*), 3.57 and 3.68 (2H, m, J=7.1 Hz, OCH_2), 4.69 (1H, s, 7-*H*, disappeared with D_2O), 5.06 (s, 1H, 10-*H*), 5.45 (1H, s, 6-*H*); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.5, 47.1, 48.5, 58.7, 59.4, 96.3, 154.8, 163.9, 166.5, 174.6.

4b: [Found: C, 77.86; H, 5.89; N, 5.18. $C_{36}H_{32}N_2O_4$ requires C, 77.68; H, 5.79; N, 5.03%]; ν_{max} (Nujol) 1683, 1782, 3360 cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 0.58 (3H, t, J=7.1 Hz, *Me*), 2.17 (6H, s, *Me*), 3.68 and 3.75 (2H, m, J=7.1 Hz, OCH_2), 4.66 (1H, s, 7-*H*, disappeared with D_2O), 5.12 (1H, s, 10-*H*), 5.39 (1H, s, 6-*H*); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.5, 47.1, 48.5, 58.7, 59.4, 96.3, 154.8, 163.9, 166.5, 174.6.

4c: [Found: C, 77.91; H, 5.87; N, 5.18. $C_{36}H_{32}N_2O_4$ requires C, 77.68; H, 5.79; N, 5.03%]; ν_{max} (Nujol) 1688, 1782, 3359cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 0.56 (3H, t, J=7.1 Hz, *Me*), 2.17 (6H, s, *Me*), 3.53 and 3.61 (2H, m, J=7.1 Hz, OCH_2), 4.65 (1H, s, 7-*H*, disappeared with

D_2O), 5.00 (1H, s, 10-*H*), 5.39 (1H, s, 6-*H*); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.1, 21.0(2), 46.1, 47.1, 57.8, 61.0, 96.6, 154.6, 163.5, 167.1, 174.9.

4d: [Found: C, 77.46; H, 5.90; N, 4.91. $C_{36}H_{32}N_2O_4$ requires C, 77.68; H, 5.79; N, 5.03%]; ν_{max} (Nujol) 1689, 1781, 3439 cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 0.55 (3H, t, *J*=7.1 Hz, *Me*), 2.23 (6H, s, *Me*), 3.52 and 3.61 (2H, m, *J*=7.1 Hz, OC*H*$_2$), 4.64 (1H, s, 7-*H*, disappeared with D_2O), 5.01 (1H, s, 10-*H*), 5.40 (1H, s, 6-*H*); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.2, 21.0(2), 46.1, 47.0, 58.9, 60.9, 96.8, 154.7, 163.8, 167.3, 174.1.

4e: [Found: C, 73.66; H, 5.53, N, 4.61. $C_{36}H_{32}N_2O_6$ requires C, 73.45; H, 5.48; N, 4.76%]; ν_{max} (Nujol) 1688, 1781, 3430 cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 0.57 (3H, t, *J*=7.1 Hz, *Me*), 3.81 (6H, s, O*Me*), 3.56 and 3.65 (2H, m, *J*=7.1 Hz, OC*H*$_2$), 4.70 (1H, s, 7-*H*, disappeared with D_2O), 5.15 (1H, s, 10-H), 5.42 (1H, s, 6-H); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.2, 46.5, 47.2, 56.2(2), 57.2, 60.9, 96.7, 155.0, 163.7, 166.8, 175.1.

4f: [Found: C, 73.41; H, 5.39; N, 4.61. $C_{36}H_{32}N_2O_6$ requires C, 73.45; H, 5.48; N, 4.76%]; ν_{max} (Nujol) 1682, 1778, 3430 cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 0.58 (3H, t, *J*=7.1 Hz, *Me*), 3.58 and 3.67 (2H, m, *J*=7.1 Hz, OC*H*$_2$), 3.65 (6H, s, O*Me*), 4.68 (1H, s, 7-*H*, disappeared with D_2O), 5.03 (1H, s, 10-*H*), 5.41 (1H, s, 6-*H*); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.3, 46.5, 48.4, 54.9(2), 58.7, 59.9, 96.3, 154.9, 163.8, 166.5, 174.8.

4g: [Found: C, 68.51; H, 4.47; N, 4.80. $C_{34}H_{26}Cl_2N_2O_4$ requires C, 68.35; H, 4.39; N, 4.69%]; ν_{max} (Nujol) 1681, 1788, 3370 cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 0.59 (3H, t, *J*=7.1 Hz, *Me*), 3.63 and 3.71 (2H, m, *J*=7.1 Hz, OC*H*$_2$), 4.64 (1H, s, 7-*H*, disappeared with D_2O), 5.03 (1H, s, 10-*H*), 5.43 (1H, s, 6-*H*); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.3, 46.5, 47.2, 58.7, 60.6, 96.4, 155.0, 164.1, 166.6, 176.0.

5a: [Found: C, 74.39; H, 5.69; N, 6.18. $C_{29}H_{26}N_2O_4$ requires C, 74.66; H, 5.62; N, 6.00%]; ν_{max} (Nujol) 1688, 1801, 3347 cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 0.60 (3H, t, *J*=7.1 Hz, *Me*), 2.48 (3H, s, *Me*), 3.70 and 3.79 (2H, m, *J*=7.1 Hz, OC*H*$_2$), 4.52 (1H, s, 7-*H*, disappeared with D_2O), 4.94 (1H, s, 10-*H*), 5.30 (1H, s, 6-*H*); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.5, 20.8, 45.8, 46.1, 58.7, 59.4, 96.1, 153.1, 163.6, 167.8, 174.7.

5c: [Found: C, 75.47; H, 6.26; N, 5.78. $C_{31}H_{30}N_2O_4$ requires C, 75.28; H, 6.11; N, 5.66%]; ν_{max} (Nujol) 1681, 1783, 3360 cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 0.61 (3H, t, *J*=7.1 Hz, *Me*), 2.20 (6H, s, *Me*), 2.55 (3H, s, *Me*), 3.80 and 3.89 (2H, m, *J*=7.1 Hz, OC*H*$_2$), 4.43 (1H, s, 7-*H*, disappeared with D_2O), 4.77 (1H, s, 10-*H*), 5.08 (1H, s, 6-*H*); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.3, 20.7(2), 21.1, 44.8, 46.2, 56.9, 58.9, 96.4, 154.0, 163.9, 167.3, 174.5.

5d: [Found: C, 75.51; H, 6.24; N, 5.48. $C_{31}H_{30}N_2O_4$ requires C, 75.28; H, 6.11; N, 5.66%]; ν_{max} (Nujol) 1687, 1779, 3368 cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 0.65 (3H, t, *J*=7.1 Hz, *Me*), 2.22 (6H, s, *Me*), 2.51 (3H, s, *Me*), 3.74 and 3.84 (2H, m, *J*=7.1 Hz, OCH_2), 4.48 (1H, s, 7-*H*, disappeared with D_2O), 4.83 (1H, s, 10-*H*), 5.25 (1H, s, 6-*H*); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.5, 19.1(2), 20.3, 44.4, 46.1, 57.8, 58.9, 94.8, 156.5, 164.9, 168.3, 173.8.

5f: [Found: C, 70.56; H, 5.69; N, 5.49. $C_{31}H_{30}N_2O_6$ requires C, 70.71; H, 5.74; N, 5.32%]; ν_{max} (Nujol) 1680, 1779, 3370 cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 0.68 (3H, t, *J*=7.1 Hz, *Me*), 2.54 (3H, s, *Me*), 3.68 (6H, s, O*Me*), 3.77 and 3.86 (2H, m, *J*=7.1 Hz, OC*H*$_2$), 4.52 (1H, s, 7-*H*, disappeared with D_2O), 4.89 (1H, s, 10-*H*), 5.23 (1H, s, 6-*H*); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.4, 20.7, 45.4, 46.2, 55.3(2), 57.9, 59.1, 96.4, 153.2, 163.3, 166.5, 173.7.

11b: [Found: C, 75.42; H, 6.23; N, 5.79. $C_{31}H_{30}N_2O_4$ requires C, 75.28; H, 6.11; N, 5.66%]; ν_{max} (Nujol) 1677, 1778, 3290, 3410 cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 0.91 (3H, t, *J*=10.8 Hz, *Me*), 2.26 (s, 6H, 2 *Me*), 2.64 (1H, dd, $J_{H9-H9'}$=18.8 Hz and J_{H9-H10}=14.3 Hz, 9-*H*), 3.21 (1H, dd, $J_{H9-H9'}$=18.8 Hz and $J_{H9'-H10}$=7.1 Hz, 9′-*H*), 3.49 (2H, s, N*H*$_2$, disappeared with D_2O), 3.91 (2H, q, *J*=10.8 Hz, OC*H*$_2$), 4.43 (1H, dd, J_{H9-H10}=14.3 Hz and $J_{H9'-H10}$= 7.1 Hz, 10-*H*), 4.80 (1H, s, 6-*H*); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.5, 20.1(2), 33.3, 43.6, 45.1, 57.8, 59.8, 93.5, 155.7, 164.5, 167.8, 175.8.

11c: [Found: C, 75.49; H, 6.20; N, 5.81. $C_{31}H_{30}N_2O_4$ requires C, 75.28; H, 6.11; N, 5.66%]; ν_{max} (Nujol) 1673, 1782, 3310, 3425 cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 0.88 (3H, t, *J*=10.8 Hz, *Me*), 2.29 (6H, s, 2*Me*), 2.69 (1H, dd, $J_{H9-H9'}$=18.8 Hz and J_{H9-H10}=14.3 Hz, 9-*H*), 3.24 (1H, dd, $J_{H9-H9'}$=18.8 Hz and $J_{H9'-H10}$=7.1 Hz, 9′-*H*), 3.53 (2H, s, NH_2, disappeared with D_2O), 3.93 (2H, q, *J*=10.8 Hz, OC*H*$_2$), 4.31 (1H, dd, J_{H9-H10}=14.3 Hz and $J_{H9'-H10}$= 7.1 Hz, 10-*H*), 4.83 (1H, s, 6-*H*); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.4, 20.6(2), 33.3, 43.9, 44.9, 58.7, 58.9, 93.4, 155.2, 163.0, 168.1, 176.0.

11e: [Found: C, 70.99; H, 5.80; N, 5.51. $C_{31}H_{30}N_2O_6$ requires C, 70.71; H, 5.74; N, 5.32%]; ν_{max} (Nujol) 1667, 1778, 3340, 3435 cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 1.02 (3H, t, *J*=10.8 Hz, *Me*), 2.65 (1H, dd, $J_{H9-H9'}$=18.8 Hz and J_{H9-H10}=14.3 Hz, 9-*H*), 3.21 (1H, dd, $J_{H9-H9'}$=18.8 Hz and $J_{H9'-H10}$=7.1 Hz, 9′-*H*), 3.68 (6H, s, O*Me*), 3.83 (2H, s, NH_2, disappeared with D_2O), 3.93 (2H, q, *J*=10.8 Hz, OC*H*$_2$), 4.35 (1H, dd, J_{H9-H10}=14.3 Hz and $J_{H9'-H10}$= 7.1 Hz, 10-*H*), 4.81 (1H, s, 6-*H*); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.6, 32.7, 43.2, 45.2, 55.0(2), 58.8, 60.1, 92.1, 156.3, 164.9, 168.6, 176.0.

11f: [Found: C, 70.81; H, 5.85; N, 5.48. $C_{31}H_{30}N_2O_6$ requires C, 70.71; H, 5.74; N, 5.32%]; ν_{max} (Nujol) 1674, 1783, 3290, 3415 cm^{-1}; δ_H (300 MHz, rt, $CDCl_3$) 0.93 (3H, t, *J*=10.8 Hz, *Me*), 2.59 (1H, dd, $J_{H9-H9'}$=18.8 Hz and J_{H9-H10}=14.3 Hz, 9-*H*), 3.29 (1H, dd, $J_{H9-H9'}$=18.8 Hz and $J_{H9'-H10}$=7.1 Hz, 9′-*H*), 3.59 (6H, s, O*Me*), 3.87 (2H, s, NH_2, disappeared with D_2O), 3.91 (2H, q, *J*=10.8 Hz, OC*H*$_2$), 4.40 (1H, dd, J_{H9-H10}=14.3 Hz and $J_{H9'-H10}$= 7.1 Hz, 10-*H*), 4.86 (1H, s, 6-*H*); δ_C (75 MHz, rt, $CDCl_3$) (selected data) 13.5, 32.9, 43.7, 45.4, 55.5(2), 58.2, 60.8, 93.1, 155.3, 163.0, 167.9, 176.0.

3.2.2. Procedure (b). A solution of isoxazol-5-one **1** (0.8 g, 5 mmol), β-ketoester **3** (5 mmol) and the appropriate aryl-aldehyde (5 mmol) in EtOH (50 mL), containing $AcONH_4$

(2 g, 25 mmol) and glacial AcOH (1 mL), was stirred at reflux for 2 h. The reaction mixture was worked up as above to give spirocompounds **4**, **5** and/or **11** (Table 1).

3.2.3. Procedure (c). β-Ketoester **3** (5 mmol) was added to a mixture of 4-arylmethyleneisoxazol-5-ones **6** (5 mmol) and the appropriate arylaldehyde (5 mmol) in EtOH (50 mL), containing $AcONH_4$ (2 g, 25 mmol) and glacial AcOH (1 mL). The reaction mixture was worked up as earlier to give spirocompounds **4**, **5** and/or **11** (Table 1).

3.3. Single-crystal X-ray diffraction studies of 5a

Crystal data: $C_{29}H_{26}N_2O_4$, fw=466.52, Monoclinic, $P2_1/n$ (ITC no. 14), a=7.212(1), b=30.142(4), c=11.059(1) Å, β=99.91(1)°, V=5025(1) Å^3, Z=4, ρ_{calc}=1.308 Mg/m^3, $F(000)$=984, μ(Mo Kα)=0.088 mm^{-1}, R_1=0.038/0.154 and wR_2=0.053/0.065 for 1250 (obs with $I>2\sigma(I)$)/4192 (all the independent) reflections, GOF=0.603, (Siemens P4), ($\lambda_{Mo\ K\alpha}$=0.71073 Å), T=293 K. Intensities were evaluated by profile fitting of a 96-steps peak scan among 2θ shells procedure[15] and then corrected for Lorentz polarization and for absorption effects by azimutal scan data.[16] Data-collection and reduction has been performed by SHELXTL package.[17] Structures was solved by a combination of standard Direct Methods[18] and Fourier synthesis, and refined by minimizing the function $\sum w(F_0^2-F_c^2)^2$ with the full matrix least-square technique based on all 4192 independent F^2[R(int)=0.0352], by using SHELXL97.[19] All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were located on the difference Fourier maps and included in the model refinement by the 'riding model' method. The methyl group C14 revealed a rotational disorder on two staggered positions with 0.5 of occupancy. An empirical extinction parameter was included in the last refinement cycles [0.0049(3)]. The last difference map showed no significant electron density residuals (ranging from −0.142 to 0.137 eÅ^{-3}). Final geometrical calculations and drawings were carried out with the PARST program[20] and the XPW utility of the Siemens package, respectively.

Further details of crystal structure of compound **5a** can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 lEZ UK (fax: +44-1223-336-033; e-mail: deposit@ccdc.cam.ac.uk), quoting the deposition no. CCDC-168111.

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