$NaBH_4$-I_2 Mediated Chemoselective Reduction of γ-Lactam and Thio-γ-lactam in Presence of Gem-dicarboxylates: An Easy Access to 1,3-Diaryl Pyrrolidines

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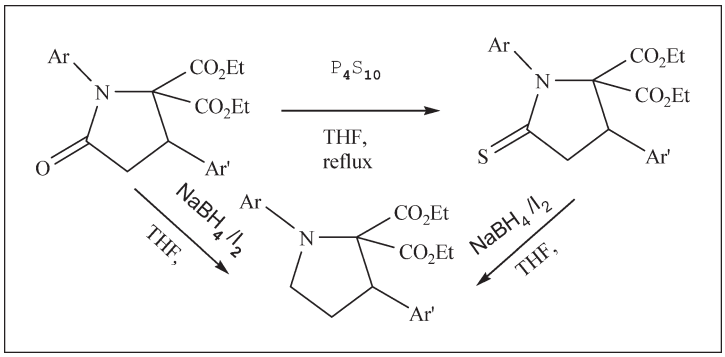

Substituted pyrrolidine derivatives were synthesized in high yield by $NaBH_4/I_2$ mediated chemoselective reduction of *N*-aryl-γ-lactam and *N*-aryl-thio-γ-lactam-2,2-dicarboxylate. With excess $NaBH_4/I_2$, carbonyl functionality of the ester groups remained unchanged.

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INTRODUCTION

Heterocycles are abundant in nature and are of great significance to life because their structural subunits exist in many natural products such as vitamins, hormones, antibiotics, and alkaloids, as well as pharmaceuticals, herbicides, dyes, and many more compounds. Among them, substituted pyrrolidines are found in numerous natural products and biologically active compounds as structural motifs [1]. Depending on the substitution pattern and functionalization, different substituted pyrrolidines have been shown to be effective antibacterials or fungicides agents and glycosidase inhibitors. A potent class of cis- and trans-di-aryl pyrrolidines that inhibit biosynthetic pathways, specially the synthesis of leukotriene-B4, can be useful for treatment of asthma, arthritis, inflammatory bowel disease, and psoriasis [2]. A series of alkaloids broussonetines A–L and broussonetinines A and B extracted from the branches of Broussonetia kazinoki (Oriental tree, termed ''himekouzo'' in Japan) have a common functionalized pyrrolidine ring system. All these compounds are strong inhibitors of α- and β-glucosidase, β-galactosidase, and α- and β-mannosidase enzymes. These compounds display different selectivity toward different enzymes [3]. Medicinal chemistry program investigated that pyrrolidines bearing an aromatic or heteroaromatic substituent at the C-3 position acts as central nervous system (CNS) stabilizers [1b].

RESULTS AND DISCUSSION

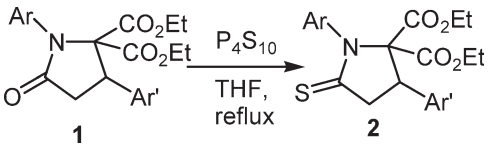
Several strategies have also been developed for the synthesis of pyrrolidines. To utilize the synthetic γ-lactams (prepared in our laboratory), we are eager to develop a chemoselective methodology to reduce the lactam carbonyl group in presence of gem-dicarboxylates for the synthesis of a pyrrolidine moiety. Chemoselective methods for the reduction of lactams to amines have also been achieved using diisobutyl aluminium hydride, diborane, sodium borohydride, and rhodium catalyzed hydrosilation [4].

As part of our on going interest in selective reduction [5] on γ-lactam derivatives, we choose $NaBH_4/I_2$ reagent system to investigate its application [6] on *N*-aryl-thio-γ-lactam derivatives [7] which are prepared from *N*-aryl-γ-lactam derivatives.

The starting material *N*-aryl-γ-lactam diesters **1a–f** was prepared following the general method [5,8,9]. The thio-γ-lactam diesters **2a–f** are prepared by refluxing the lactam with P_4S_{10} [10] in dry THF for 6 h (Scheme 1 and Table 1).

Some thio-lactams have also been found to be CNS active. These compounds cause clonic and tonic convulsions in mice a few seconds after ip (intraperitoneal) injection. The five-membered thio-lactam can cause mild sedation at lower doses (500 mg/kg) and convulsions at higher doses (1000 mg/kg) [11].

Scheme 1



Formation of BH_3: THF *in situ* by the reaction of $NaBH_4$ with I_2 in dry THF has already been reported [12] and when we treated the resulting lactams with $NaBH_4/I_2$ in dry THF which furnished substituted pyrrolidines **3a–f** in good yields (Scheme 2 and Table 2).

In presence of excess $NaBH_4/I_2$ in dry THF, carbonyl functionality of the ester groups remain unchanged.

As the mechanism of the reaction is uncertain and as we are unable to isolate the intermediate, the plausible mechanism may be written as depicted in Scheme 3 [12].

All the compounds were characterized by interpretation of the usual spectroscopic and analytical data.

CONCLUSION

Thus 1,3-diaryl pyrrolidine can be prepared by chemoselective reduction of carbonyl and thio carbonyl group of *N*-aryl-γ-lactam and *N*-aryl-thio γ-lactam by $NaBH_4$-I_2 in dry THF. Here we successfully disclose the applicability of $NaBH_4$-I_2 reagent system on lactam-carbonyl group as well as thio-lactam carbonyl group in dry THF. As pyrrolidine is the precursor of pyrrole this methodology has been successfully applied to the synthesis of a range of *N*-aryl-pyrroles.[5]

EXPERIMENTAL

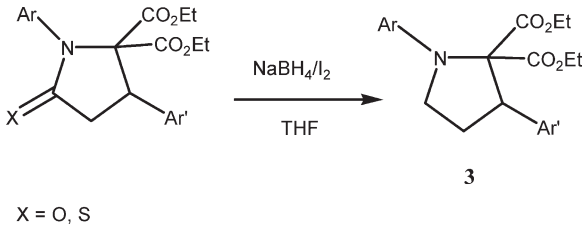
^{1}H NMR spectra were recorded in $CDCl_3$ with TMS as the internal standard on a BRUKER-AC 200 MHz and 400 MHz spectrometer. Chemical shifts are reported in ppm. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constant (Hz). ^{13}C NMR (50 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a BRUKER-AC 200 MHz and 400 MHz Spectrometer with complete proton decoupling. IR spectra were recorded on a Perkin-Elmer 883 and Shimadzu FTIR-8300 infrared spectrometers. EIMS (70 eV) spectra were taken using a VG Auto spec M mass spectrometer, and ESI-MS spectra were taken using Waters LCT mass spectrometer. All reagents and solvents are obtained from commercial suppliers.

Table 1

Synthesis of 1,3-diaryl-5-thioxopyrrolidine-2,2-dicarboxylates **2(a–f)** from 1,3-diaryl-2,2-dicarbethoxy-5-oxo-pyrrolidine **1(a–f).**

Substrate 5-oxo-pyrolidine	Ar	Ar′	5-thiooxo-pyrolidine	Yield (%)
1a	4-F-C_6H_4	Phenyl	**2a**	85
1b	4-Cl-C_6H_4	Phenyl	**2b**	83
1c	4-CH_3-C_6H_4	Phenyl	**2c**	77
1d	3,4-F,F-C_6H_3	Phenyl	**2d**	90
1e	4-F-C_6H_4	2-Thienyl	**2e**	78
1f	4-F-C_6H_4	2-Furyl	**2f**	80

Scheme 2



Chromatographic purification was done with either 60–120 or 100–200 mesh silica gels (SRL). Petroleum ether refers to the fraction boiling in the range 60–80°C. Tetrahydrofuran was freshly distilled over sodium-benzophenone.

General procedure for synthesis of diethyl *N*-aryl-5-thioxo-3-aryl/heteroaryl-pyrrolidine-2,2-dicarboxylates 2a–f. To a stirred solution of γ-lactam diester (1 mmol) in dry THF (30 mL), P_4S_{10} (3 mmol) was added under argon atmosphere, and the reaction mixture was refluxed for 5 h. Solvent was evaporated under vacuum, and the residue basified with ammonia solution. The aqueous layer then extracted with $CHCl_3$ and the combined organic layer was washed with brine and followed by water several times, dried over anhydrous Na_2SO_4 and concentrated in vacuum. Light yellow solid appeared. The product was purified by column chromatography.

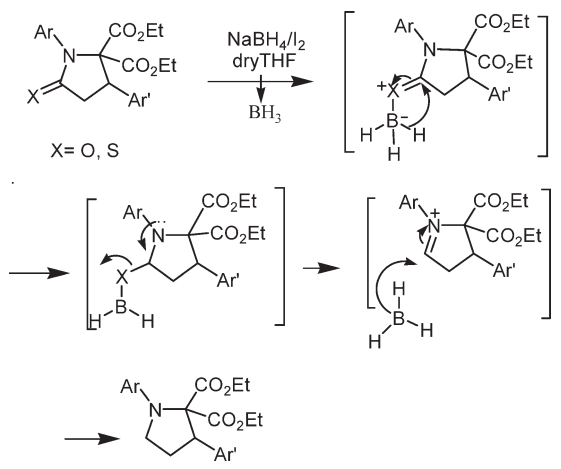
Diethyl 1-(4-fluorophenyl)-5-thioxo-3-phenyl-pyrrolidine-2,2-dicarboxylate 2a. White solid; yield 85%; mp 105–106°C (from ethyl acetate-petroleum ether); (Found: C, 63.94; H, 5.43; N, 3.21. Calculated for $C_{22}H_{22}FNO_4S$: C, 63.61; H, 5.30; N. 3.37%); ν_{max} (liquid film)/cm 1729.70, 1508.41; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.78 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 0.96 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 3.48–3.6 (m, 3H, $NCSCH_2$, $OC(H)HCH_3$), 3.85–3.95 (m, 2H, OCH_2CH_3), 4.08–4.17 (m, 1H, $OC(H)HCH_3$), 4.74 (t, 1H, J = 9.3 Hz,

Table 2

Synthesis of 1,3-diaryl-pyrrolidine-2,2-dicarboxylates **3(a-f).**

Substrate 5-oxo-/5-thio-oxo pyrolidine	Ar	Ar′	Product	Yield (%)
1a	4-F-C_6H_4	Phenyl	**3a**	84
2a	4-F-C_6H_4	Phenyl	**3a**	82
1b	4-Cl-C_6H_4	Phenyl	**3b**	83
2b	4-Cl-C_6H_4	Phenyl	**3b**	80
1c	4-CH_3-C_6H_4	Phenyl	**3c**	77
2c	4-CH_3-C_6H_4	Phenyl	**3c**	65
1d	3,4-F,F-C_6H_3	Phenyl	**3d**	83
2d	3,4-F,F-C_6H_3	Phenyl	**3d**	81
1e	4-F-C_6H_4	2-Thienyl	**3e**	78
2e	4-F-C_6H_4	2-Thienyl	**3e**	62
1f	4-F-C_6H_4	2-Furyl	**3f**	82
2f	4-F-C_6H_4	2-Furyl	**3f**	86

Scheme 3



C(3)*H*Ph), 7.07–7.17 (m, 2H, Ar-*H*), 7.22–7.37 (m, 7H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.26, 13.42 (2× OCH_2CH_3), 47.70 (NCSCH_2), 47.87 (C(3)Ph), 62.14, 62.63 (2× OCH_2CH_3), 85.42 (*C*(2)), 115.92, 116.38, 128.29, 128.36, 128.56, 130.65, 130.83, 135.36, 135.61, 160.01 (Ar*C*), 165.71, 166.06 (2× *C*OOCH_2CH_3), 207.29 (N*C*S).

Diethyl 1-(4-chlorophenyl)-5-thioxo-3-phenyl-pyrrolidine-2,2-dicarboxylates 2b. Light yellow crystalline solid; yield 83%; mp 135–136°C (from ethylacetate-petroleum ether); (Found: C, 61.04; H, 4.97; N, 3.16. Calculated for $C_{22}H_{22}ClNO_4S$: C, 61.18; H, 5.09; N, 3.24%) ν_{max} (liquid film)/cm 1733.14, 1490.68; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.77 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 0.96 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 3.47–3.59 (m, 3H, NCSCH_2, OC(*H*)HCH_3), 3.84–3.96 (m, 2H, OCH_2CH_3), 4.09–4.14 (m, 1H, OC(*H*)HCH_3), 4.72 (t, 1H, J = 9.3 Hz, C(3)*H*Ph), 7.19–7.42 (m, 9H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.25, 13.40 (2× OCH_2CH_3), 47.73 (NCSCH_2), 47.97 (*C*(3)Ph), 62.17, 62.68 (2× OCH_2CH_3), 85.34 (*C*(2)), 128.34, 128.55, 129.40, 130.28, 134.91,135.59, 138.00 (Ar*C*), 165.65, 166.00 (2× *C*OOCH_2CH_3), 207.15 (N*C*S). ESI-MS for $C_{22}H_{22}NO_4SCl$ [M],[M + H+]: 432.10 (^{35}Cl); 434.10 (^{37}Cl).

Diethyl 1-(*p*-tolyl)-5-thioxo-3-phenyl-pyrrolidine-2,2-dicarboxylate 2c. White crystalline solid; yield 77%; mp 118–120°C (from ethyl acetate-petroleum ether); (Found: C, 67.52; H, 6.05; N, 3.44. Calculated for $C_{23}H_{25}NO_4S$: C, 67.15; H, 6.08; N, 3.40); ν_{max} (liquid film)/cm 1729.83, 1511.40; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.78 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 0.92 (3H, t, J = 7.1 Hz, OCH_2CH_3), 2.36 (3H, s, ArCH_3), 3.49–3.60 (m, 3H, NCSCH_2, OC(*H*)HCH_3), 3.61–3.94 (m, 2H, OCH_2CH_3), 3.98–4.14 (m, 1H, OCH_2CH_3), 4.74 (t, 1H, J = 9.3 Hz, C(3)*H*Ph)), 7.1–7.25 (m, 5H, Ar-*H*), 7.28–7.42 (m, 4H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.27, 13.30 (2× OCH_2CH_3), 21.22 (ArCH_3), 47.69 (NCSCH_2), 47.89 (*C*(3)Ph), 61.98, 62.51 (2× OCH_2CH_3), 85.47 (*C*(2)), 128.18, 128.28, 128.34, 128.49, 129.80, 135.73, 136.86, 138.90 (Ar*C*), 165.78, 166.04 (2× *C*OOCH_2CH_3), 206.83 (N*C*S). ESI-MS for $C_{23}H_{25}NO_4S$ [M],[M + H^+]: 412.13.

Diethyl 1-(3,4-difluoro phenyl)-5-thioxo-3-phenyl-pyrrolidine-2,2-dicarboxylate 2d. Light yellow crystalline solid; yield 90%; mp 78–83°C (from ethyl acetate-petroleum ether); ν_{max} (liquid film)/cm 1736.14, 1509.61; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.77 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.00 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 3.48–3.56 (dd, 2H, J = 8.8, 22.4 Hz, NCSCH_2), 3.84–3.91 (m, 1H, OCH_2CH_3), 3.92–4.00 (1H, m, OCH_2CH_3)), 4.11–4.21 (1H, m, OCH_2CH_3), 4.24–4.29 (1H, m, OCH_2CH_3)), 4.72 (t, 1H, J = 9.2 Hz, C(3)*H*Ph), 6.94–7.04 (m, 1H, Ar-*H*)), 7.17–7.21 (m, 2H, Ar-*H*), 7.24–7.31 (m, 5H, Ar-*H*). δC (100 MHz; $CDCl_3$; Me_4Si) 13.29, 13.55 (2× OCH_2CH_3), 47.76 (NCSCH_2), 47.92 (*C*(3)Ph), 62.41, 62.85 (2× OCH_2CH_3), 85.37 (*C*(2)), 117.44, 117.62, 17.81, 118.83, 119.01, 125.78, 125.81, 128.41, 128.45, 128.67, 135.52, 135.58, 165.60 (Ar*C*), 166.06, 167.31 (2× *C*OOCH_2CH_3), 207.51 (N*C*S). $C_{22}H_{21}NO_4F_2S$ [M],[M + H+]:434.19.

Diethyl 1-(4-fluoro phenyl)-5-thioxo-3-(2-thienyl)-pyrrolidine-2,2-dicarboxylate 2e. Light yellow crystalline solid; yield 78%; mp 112–1116°C (from ethyl acetate-petroleum ether); (Found: C, 57.03; H, 4.87; N. 3.29. Calculated for $C_{20}H_{20}NO_4FS_2$: C, 57.04; H, 4.78; N. 3.32%); ν_{max} (liquid film)/cm 1733.14, 1498.88; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si): δ 0.92 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 0.98 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 3.55–3.78 (m, 2H, NCSCH_2), 3.91–3.97 (m, 1H, OCH_2CH_3), 4.00–4.04 (m, 2H, OCH_2CH_3), 4.05–4.16 (m, 1H, OCH_2CH_3), 4.96–5.01 (dd, 1H, J = 8.4, 11.2 Hz, C(3)*H*), 6.99–7.04 (m, 2H, Ar-*H*), 7.08–7.15 (m, 2H, Ar-*H*), 7.24–7.29 (m, 3H, Ar-*H*). ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si): δ 13.40 (2× OCH_2CH_3), 43.38 (NCSCH_2), 48.46 (C(3)), 62.42, 62.61 (2× OCH_2CH_3), 84.89 (*C*(2)), 116.13, 116.36, 125.55, 126.56, 126.90, 130.40, 130.48, 135.30, 135.33, 137.42, 161.22, 163.70 (Ar*C*), 165.17, 165.90 (2× *C*OOCH_2CH_3), 206.12 (N*C*S). $C_{20}H_{20}NO_4FS_2$ [M],[M + H^+]: 422.16.

Diethyl 1-(4-fluorophenyl)-5-thioxo-3-(2-furyl)-pyrrolidine-2,2-dicarboxylate 2f. Light yellow crystalline solid; yield 80%; mp 133–134°C (from ethyl acetate-petroleum ether); (Found: C, 57.62; H, 4.85; N, 3.31. Calculated for $C_{20}H_{20}NO_5FS$: C, 56.99; H, 4.78; N. 3.32%); ν_{max} (liquid film)/cm 1735.85, 1508.40; ^{1}H NMR (400 MHz; $CDCl_3$; Me_4Si): δ 0.92 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.00 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 3.43–3.74 (m, 2H, NCSCH_2), 3.76–3.81 (m, 1H, OCH_2CH_3), 3.85–4.05 (m, 1H, OCH_2CH_3), 4.06–4.12 (m, 2H, OCH_2CH_3), 4.76–4.81 (dd, 1H, J = 8.8, 11.6 Hz, C(3)*H*), 6.28–6.33 (dd, 2H, J = 2.8, 19.2 Hz, Ar-*H*), 6.96–7.09 (m, 2H, Ar-*H*), 7.11–727 (m, 2H, Ar-*H*), 7.37 (s, 1H, Ar-*H*). ^{13}C NMR (100 MHz; $CDCl_3$; Me_4Si): δ 13.46, 13.52 (2× OCH_2CH_3), 42.26 (NCSCH_2), 45.84 (*C*(3)), 62.74, 62.78 (2× OCH_2CH_3), 83.68 (*C*(2)), 109.08, 110.60, 115.95, 116.09, 130.50, 130.58, 135.03, 135.06, 142.69, 148.68, 161.20, 163.28 (Ar*C*), 164.98, 165.89 (2× *C*OOCH_2CH_3), 205.91 (N*C*S). $C_{20}H_{20}NO_5FS$ [M],[M + H^+]: 406.17.

General procedure for the synthesis of 1-aryl-2,2-dicarbethoxy-3-aryl/heteroarylpyrrolidine 3(a–f) from diethyl 1,3-diaryl-5-oxo-pyrrolidine-2,2-dicarboxylates 1(a–f). To a stirred solution of $NaBH_4$ (4 mmol) in dry THF (20 mL), a solution of iodine (3 mmol) in dry THF (5 mL) was added drop wise under an argon atmosphere at 0°C over 45 min. Next γ-lactam diester (1 mmol) in dry THF (5 mL) was added to the reagent mixture, which was stirred at 25–30°C for 2 h. Then the mixture was refluxed for 20 min, cooled to 0°C, and the excess hydride was carefully destroyed with dilute HCl solution and then neutralized with dilute NaOH solution. The organic layer was separated, and the aqueous layer was extracted

with ether. The combined organic extracts were washed with sodium thiosulfate solution and then with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude products were purified by column chromatography. Colorless viscous oily materials were identified by spectroscopic methods.

General procedure for the synthesis of 1-aryl-2,2-dicarbethoxy-3-aryl/heteroarylpyrrolidine 3(a–f) from diethyl *N*-aryl-5-thioxo-3-aryl/heteroaryl-pyrrolidine-2,2-dicarboxylates (2a–f). To a stirred solution of $NaBH_4$ (3 mmol) in dry THF (20 mL), solution of iodine (2 mmol) in dry THF (5 mL) was added drop by drop, under an argon atmosphere at 0°C. The thio-γ-lactam diester (1 mmol) in dry THF (5 mL) was added to the mixture and next the resulting reaction mixture was stirred for 3–5 h at room temperature (25–30°C). After completion, the reaction (checking by TLC), the reaction mixture was cooled to 0°C, and excess hydride was carefully destroyed by adding dilute HCl solution. Then it was neutralized with dilute NaOH solution. The organic layer was evaporated out under reduced pressure and the aqueous layer was extracted with ether. The combined organic layer was washed with sodium thiosulfate solution and then with brine and dried over anhydrous Na_2SO_4. The solvent was evaporated, and the crude products were purified by column chromatography. Colorless viscous oily materials were identified by spectroscopic methods.

1-(4-Fluorophenyl)-2,2-dicarbethoxy-3-phenyl pyrrolidine 3a. Yellow viscous oily material; yield (84% from 1a; 82% from 2a); (Found: C, 68.66; H, 6.25; N, 3.61. Calculated for $C_{22}H_{24}FNO_4$: C, 68.56; H, 6.28; N, 3.63%); ν_{max} (liquid film)/cm 1726.24; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.85 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.12 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.42–2.51 (m, 2H, C(4)H_2), 3.63–3.86 (m, 4H, OCH_2CH_3), 4.09–4.25 (m, 3H, C(5)H_2, C(3)*H*), 6.58–6.65 (m, 2H, Ar-*H*), 6.84–6.93 (m, 2H, Ar-*H*), 7.20–7.35 (m, 5H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.869, 14.117 (2× OCH_2CH_3), 29.61 (*C*(4)), 50.31(*C*(5)), 54.85 (*C*(3)), 61.20, 61.62 (2× OCH_2CH_3), 114.58 (*C*(2)), 115.020, 115.59, 115.74, 153.79, 158.48 (Ar*C*), 168.18, 169.43 (2× $COOCH_2CH_3$).

1-(4-Chlorophenyl)-2,2-dicarbethoxy-3-phenyl pyrrolidine 3b. Yellow viscous oily material; yield (83% from 1b; 80% from 2b); (Found: C, 65.68; H, 5.99; N, 3.51. Calculated for $C_{22}H_{24}ClNO_4$: C, 65.75; H, 6.02; N, 3.49%); ν_{max} (liquid film)/cm 1729.25; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.87 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 1.16 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 2.38–2.57 (m, 2H, C(4)H_2), 3.64–3.91(m, 4H, OCH_2CH_3), 4.14–4.24 (3H, m, C(5)H_2, C(3)H), 6.54–6.62 (m, 2H, Ar-*H*), 7.09–7.17 (m, 2H, Ar-*H*), 7.21–7.34 (m, 5H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.49, 13.97 (2× OCH_2CH_3), 28.94 (*C*(4)), 50.07 (C(5)), 55.06 (*C*(3)), 61.37, 61.84 (2× OCH_2CH_3), 115.47 (*C*(2)), 122.78, 128.22, 128.30, 128.46, 137.88, 144.31 (Ar*C*), 167.87, 169.40 (2× $COOCH_2CH_3$).

1-(*p*-Tolyl)-2,2-dicarbethoxy-3-phenyl pyrrolidine 3c. Yellow viscous oily material; yield (77% from 1c; 65% from 2c); (Found: C, 72.51; H, 7.10; N, 3.65. Calculated for $C_{23}H_{27}NO_4$: C,72.42; H, 7.13; N, 3.67%); ν_{max} (liquid film)/cm 1735.17; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.90 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.17 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.27 (s, 3H, Ar-CH_3), 2.41–2.57 (m, 2H, C(4)H_2), 3.66–3.95 (m, 4H, OCH_2CH_3), 4.20 (q, 3H, J = 7.4 Hz, C(5)H_2, C(3)*H*), 6.63 (d, 2H, J = 8.4 Hz, Ar-*H*), 7.01–7.05 (d, 2H, J = 8.1 Hz, Ar-*H*), 7.27–7.32 (m, 5H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.35, 13.78 (2× OCH_2CH_3), 20.15 (ArCH_3), 28.81 (*C*(4)), 49.74 (*C*(5)), 54.80 (*C*(3)), 60.94, 61.38 (2× OCH_2CH_3), 114.25 (*C*(2)), 126.69, 127.35, 127.97, 128.29, 128.82, 138.02, 143.21 (Ar*C*), 168.11, 169.60 (2× $COOCH_2CH_3$).

1-(3,4-Difluorophenyl)-2,2-dicarbethoxy-3-phenyl pyrrolidine 3d. Yellow viscous oily material; yield (83% from 1d; 81% from 2d); (Found: C, 65.62; H, 5.73; N, 3.50. Calculated for $C_{22}H_{23}F_2NO_4$: C, 65.50; H, 5.75; N, 3.47 %.); ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.85 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.16 (t, 3H, J = 7.1 Hz, OCH_2CH_3), 2.38–2.47 (m, 2H, C(4)H_2), 3.61–3.91 (m, 4H, OCH_2CH_3), 4.14–4.25 (m, 3H, C(5)H_2, C(3)*H*), 6.26–6.33 (m, 1H, Ar-*H*), 6.43–6.55 (m, 1H, Ar-*H*), 6.87–7.02 (m, 1H, Ar-*H*), 7.19–7.33 (m, 5H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.45, 13.93 (2× OCH_2CH_3), 28.87 (*C*(4)), 50.35 (*C*(5)), 54.97 (*C*(3)), 61.47, 61.92 (2× OCH_2CH_3), 103.35, 103.78, 109.49, 109.55 (Ar*C*), 116.40 (*C*(2)), 116.74, 127.70, 128.24, 128.39, 137.75, 140.80, 141.06, 142.52, 142.72, 145.52, 145.78, 147.51, 147.78, 152.36, 152.63 (Ar*C*), 167.79, 169.22 (2× $COOCH_2CH_3$).

1-(4-Fluorophenyl)-2,2-dicarbethoxy-3-(2-thienyl) pyrrolidine 3e. Yellow viscous oily material; yield (78% from 1e; 62% from 2e); (Found: C, 61.48; H, 5.63; N, 3.56. Calculated for $C_{20}H_{22}FNO_4S$: C, 61.37; H, 5.66; N, 3.58%); ν_{max} (liquid film)/cm 1726.40; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 0.97 (t, 3H, J = 6.9 Hz, OCH_2CH_3), 1.17 (t, 3H, J = 6.9 Hz, OCH_2CH_3), 2.46–2.54 (m, 2H, C(4)H_2), 3.69–3.82 (m, 2H, OCH_2CH_3), 3.86–3.99 (m, 2H, OCH_2CH_3), 4.14–4.25 (m, 2H, C(5)H_2), 4.45 (dd, 1H, J = 7.5, 9.8 Hz, C(3)*H*), 6.57–6.64 (m, 2H, Ar-*H*), 6.83–6.96 (m, 4H, Ar-*H*), 7.19–7.22 (m, 1H, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.64, 13.95 (2× OCH_2CH_3), 30.64 (*C*(4)), 50.10 (*C*(5)), 50.23 (*C*(3)), 61.55, 61.84 (2× OCH_2CH_3), 114.64 (*C*(2)), 115.08, 115.39, 115.54, 124.73, 126.38, 126.57, 140.45, 142.13, 142.16, 153.73, 158.43 (Ar*C*), 168.15, 169.15 (2× $COOCH_2CH_3$).

1-(4-Fluorophenyl)-2,2-dicarbethoxy-3-(2-furyl) pyrrolidine 3f. Yellow viscous oily material; yield (82% from 1f; 86% from 2f); (Found: C, 64.07; H, 5.88; N, 3.75. Calculated for $C_{20}H_{22}FNO_5$: C, 63.99; H, 5.91; N, 3.73%); ν_{max} (liquid film)/cm 1736.16; ^{1}H NMR (200 MHz; $CDCl_3$; Me_4Si): δ 1.02 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 1.14 (t, 3H, J = 7.2 Hz, OCH_2CH_3), 2.34–2.52 (m, 2H, C(4)H_2), 3.67–3.74 (m, 2H, OCH_2CH_3), 3.80–4.01 (m, 2H, OCH_2CH_3), 4.12–4.34 (m, 3H, C(5)H_2, C(3)*H*), 6.18 (d, 1H, J = 3 Hz, Ar-*H*), 6.30 (t, 1H, J = 1.9 Hz, Ar-*H*), 6.55–6.62 (m, 2H, Ar-*H*), 6.83–6.91 (2H, m, Ar-*H*), 7.34 (d, 1H, J = 1.8 Hz, Ar-*H*). ^{13}C NMR (50 MHz; $CDCl_3$; Me_4Si): δ 13.69, 13.86 (2× OCH_2CH_3), 27.59 (*C*(4)), 48.75 (*C*(5)), 49.89 (*C*(3)), 61.59, 61.82 (2× OCH_2CH_3), 107.62, 110.24, 114.61 (*C*(2)), 115.05, 115.12,115.27, 141.92, 151.63, 153.67, 158.37 (Ar*C*), 168.22, 169.07 (2× $COOCH_2CH_3$).

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REFERENCES AND NOTES

[1] (a) Zhongze, M.; Yoshio, H.; Feng, Q.; Yingjie, C.; Taro, N. Tetrahedron Lett 2004, 45, 3263; (b) Sonesson, C.; Wikström, H.; Smith, M. W.; Svensson, K.; Carlsson, A.; Waters, N. Bioorg Med Chem Lett 1997, 7, 241.

[2] Yee, N. K.; Nummy, L. J.; Byrne, D. P.; Smith, L. L.; Roth, G. P. J Org Chem 1998, 63, 326.

[3] O'Hagan, D. Nat Prod Rep 2000, 17, 435.

[4] Flaniken, J. M.; Collins, C. J.; Lanz, M.; Singaram, B. Org Lett 1999, 1, 799.

[5] (a) Haldar, P.; Ray, J. K. Org Lett 2005, 7, 4341; (b) Haldar, P.; Ray, J. K. Tetrahedron Lett 2003, 44, 8229.

[6] (a) Haldar, P.; Guin, J.; Ray, J. K. Tetrahedron Lett 2005, 46, 1071; (b) Haldar, P.; Barman, G.; Ray, J. K. Tetrahedron 2007, 63, 3049.

[7] Sabeena, M. S.; Pakrashi, S. C.; Giri, V. S.; Mandal, S. B. J Org Chem 1988, 53, 4236.

[8] (a) Kar, G. K.; Ramesh, D.; Chatterjee, B. G.; Ray, J. K. J Chem Res (M) 1997, 568; (b) Kar, G. K.; Ramesh, D.; Chatterjee, B. G.; Ray, J. K. J Chem Res (S) 1997, 80.

[9] (a) Ray, J. K.; Sami, I.; Kar, G. K.; Roy, B. C.; Brahma, N. K. Bioorg Med Chem 1994, 2, 1417; (b) Kar, G. K.; Roy, B. C.; Das Adhikari, S.; Ray, J. K.; Brahma, N. K. Bioorg Med Chem 1998, 6, 2397; (c) Chatterjee, B. G.; Sahu, D. P. J Org Chem 1977, 42, 3162.

[10] Polshettiwar, V.; Kaushik, M. P. Tetrahedron Lett 2004, 45, 6255.

[11] Lien, E. J.; Tong, G. L. J Med Chem 1971, 14, 846.

[12] Prasad, A. S. B.; Kanth, J. V. B.; Periasamy, M. Tetrahedron 1992, 48, 4623.