

Expedient Access to an *N*-phenylpyrrolidin-2-yl Heterocycle via a Base-Induced Intramolecular *aza*-Michael Reaction

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ABSTRACT

Ethyl 2-(1-phenylpiperidin-2-yl) acetate was formed in a spontaneous cyclization from (E)-ethyl 7-oxohept-2-enoate whereas ethyl [1-(2-bromophenyl)-2-pyrrolidinyl] acetate could be synthesized in good overall yield when employing a stoichiometric amount of base to facilitate the intramolecular *aza*-Michael reaction.

KEYWORDS

aza Michael, intramolecular, catalysed, piperidine, pyrrolidine, base.

1. Introduction

Compounds with biological activity are often derived from nitrogen-heterocyclic structures, which also appear frequently in natural products.¹ A vast number of natural and synthetic *N*-heterocyclic compounds have found applications as pharmaceuticals and agricultural chemicals. Nitrogen-heterocycles pertinent to this communication include *N*-phenylpyrrolidines and *N*-phenylpiperidine (Fig. 1).

As a result, a variety of synthetic methodologies for these structures have been developed and many reviews^{2–6} and monographs^{7–9} have been released.

Under certain conditions, direct (uncatalysed) nucleophilic addition of amines can proceed at electron deficient (activated) π -systems containing neighbouring functional groups such as keto, ester, nitrile, sulfoxide and nitro.^{10–13} These reactions occur exclusively at the β -position and are sometimes referred to as *aza*-Michael additions (Scheme 1).^{14,15}

Addition of less reactive amines can proceed efficiently using Brønsted acids (e.g. H₂SO₄,¹⁶ HCl,^{17,18} acetic acid,^{19,20} boric acid²¹ or bis(trifluoromethanesulfonyl)imide^{22,23}) as catalyst. On the other hand, simple organic bases can also facilitate these additions in almost quantitative yields.^{24–26} The intramolecular *aza* Michael reaction (IMAMR) offers a direct and atom-economical means of efficiently synthesizing nitrogen heterocycles. The intramolecular addition of weakly nucleophilic carbamates and amides to α,β -unsaturated esters can be induced using potassium *tert*-butoxide (Scheme 2).²⁷ The cyclization of **1** leading to the stereodivergent synthesis of 2,3-disubstituted piperidines **2** and **3** was accomplished in high yields and de's.

Milder bases were employed catalytically for the 1,4-conjugate addition of pyrroles and indoles to pendant unsaturated esters **4**.²⁶ Using DABCO, (-) sparteine or K₂CO₃, racemic heterocyclic products **5** can be obtained in good to excellent yields (Scheme 3).

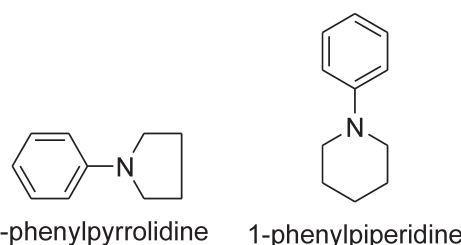


Figure 1 Nitrogen heterocycles.

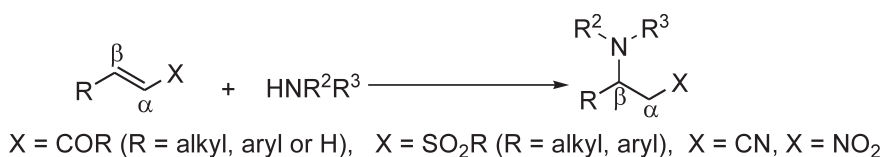
Despite the wide availability of synthetic methods, there still exists a need to develop more efficient procedures, particularly those that allow the synthesis of complex azapolycyclic ring-systems. Herein, we report an efficient and simple synthetic route to ethyl 2-(1-phenylpiperidin-2-yl) and ethyl 2-(1-phenylpyrrolidin-2-yl) acetates *via* a base-induced intramolecular *aza*-Michael reaction as the key C-N bond forming step.

3. Results and Discussion

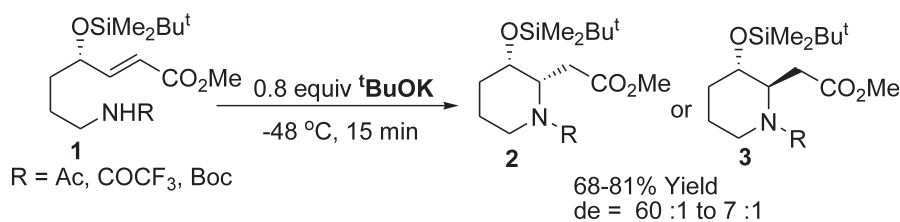
Synthesis of the target molecule started from a lactol, derived from the acid catalysed hydrolysis of a cyclic enol-ether.²⁸ The product tetrahydropyran-2-ol exists in a tautomeric equilibrium with 5-hydroxypentanal (Scheme 4).

The first step towards the synthesis of the amino α,β -unsaturated ester substrates began with the HWE reaction between the 5 or 6 membered lactol and requisite phosphonium ylide **6** (Scheme 5). Synthesis of **7** proceeded smoothly to afford the hydroxy α,β -unsaturated ester in good yield. In contrast, the formation of **8** required more forcing conditions and a longer reaction time to obtain the Wittig product in good yield. Both products **7** and **8** were formed with predominately *E*-selectivity (>96 %) as determined by ¹H NMR spectroscopy: denoted by the presence of two signals exhibiting a splitting pattern of double triplets at 6.95 ppm (*J* 7.2 and 15.6 Hz) and 5.85 ppm (*J* 1.6 and 15.6 Hz). All ¹H and ¹³C signals were unambiguously

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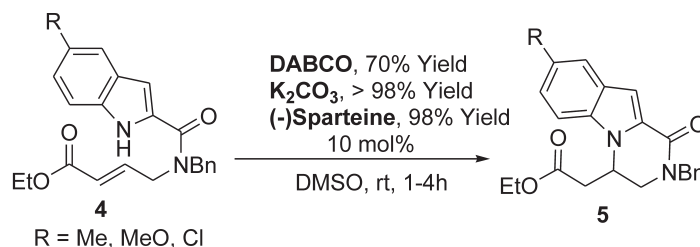


Scheme 1
aza-Michael Reaction.



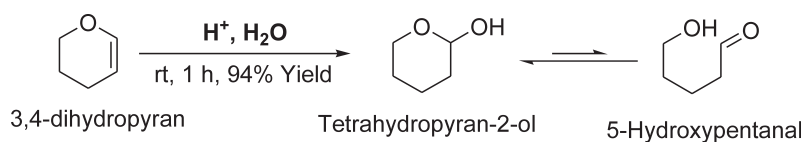
Scheme 2

^tBuOK-induced cyclization of amides and carbamates to α , β -unsaturated esters.



Scheme 3

Base-catalysed intramolecular *aza*-Michael reaction of indoles containing pendant-conjugated esters.



Scheme 4

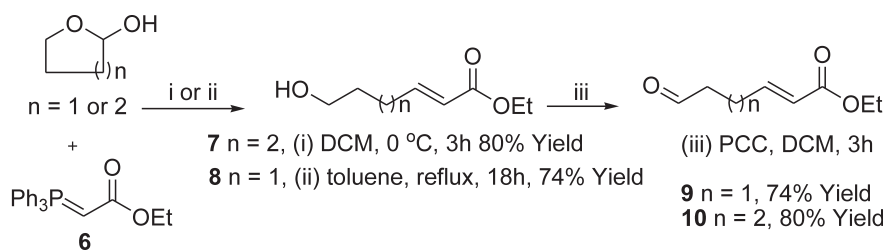
Synthesis of pyran-2-ol.

assigned and correlated well with literature values.^{29,30} Primary alcohols **7** and **8** were converted to the corresponding aldehydes **9** and **10** by PCC oxidation in good yields. The success of the oxidation was confirmed by observation of the singlet resonances (9.78 to 9.79 ppm) in the ¹H NMR spectrum corresponding to the aldehyde hydrogen. Products **9** and **10** were used immediately in the next step.

In order to prepare the target molecule, a reductive amination reaction between aldehyde **10** and aniline was initially attempted (Scheme 6). Using NaBH(OAc)₃ as reducing agent, the imine formed between aniline and aldehyde **10** was reduced to the desired secondary amine **12** with accompanying IMAMR product **11**. Compound **11** was obtained in modest yield after separation by chromatography and fully characterized by FT-IR,

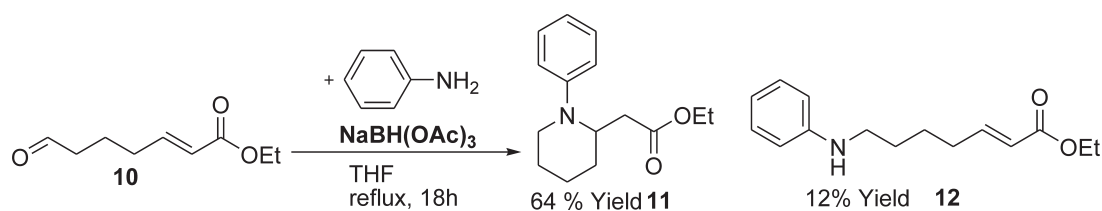
¹H and ¹³C NMR spectroscopy and mass spectrometry. Compound **12** was identified by the absence of the aldehyde signal (9.78 ppm) and appearance of a broad singlet corresponding to the amino group (3.63 ppm) in the ¹H NMR spectrum. The formation of **11** was attributed to a Brønsted acid-catalysed cyclization during the acidic work up with aqueous HCl and therefore negated the need to explore the base-induced cyclization given that it apparently proceeds reasonably well under acidic conditions.

At this stage we decided to move forward with the synthesis using 2-bromoaniline given that it was available in our laboratory and that the bromo functionality could potentially be further exploited for further derivatization. The 2-bromo-substituted aryl amino compound **13** was prepared by reductive



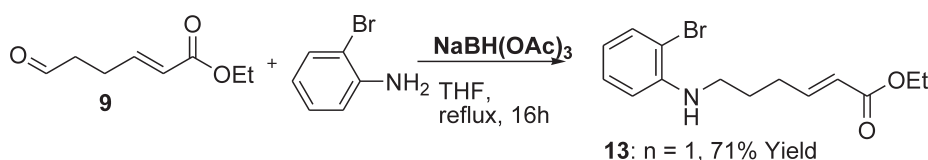
Scheme 5

Synthesis of aldehyde intermediates.

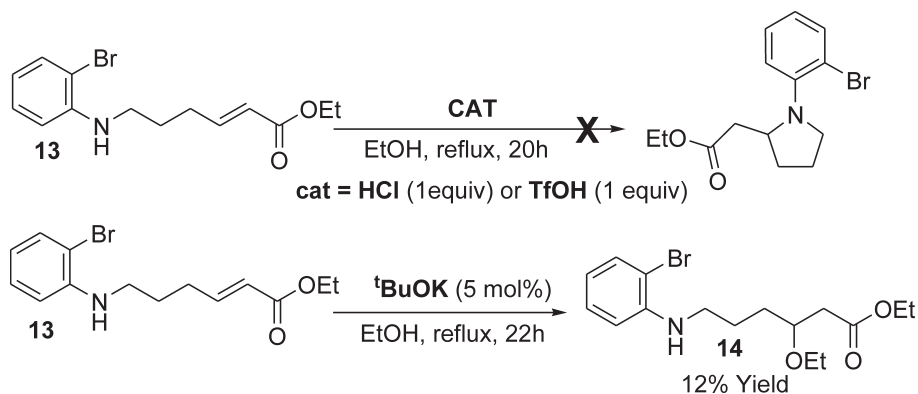


Scheme 6

Reductive amination reaction.



Scheme 7
Reductive amination reaction.



Scheme 8
Examination of acid and base-induced IMAMR.

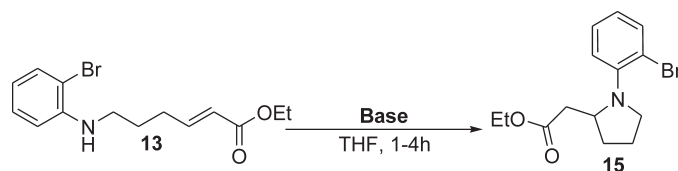
amination of **9** with 2-bromoaniline (Scheme 7). The expected product of the reductive amination reaction was obtained in good yield, and its structure was confirmed by the absent aldehyde resonance (9.78 ppm) in the ^1H NMR spectrum, and appearance of the C-Br resonance (109.7 ppm) in the ^{13}C NMR spectrum.

To verify that the cyclization could be mediated under acidic conditions we initially refluxed substrate **13** in ethanol and hydrochloric acid for 20 hours and in another experiment using TfOH (Scheme 8). Only the starting material was recovered and no IMAMR products were observed. A catalytic amount of potassium *tert*-butoxide was also unsuccessful in producing the cyclized product. Furthermore, in addition to recovering most of the unreacted starting material, compound **14** corresponding to an *oxa*-Michael addition of ethanol to **13**, was isolated by chromatography. The compound exhibits a distinctive *CH* methine resonance in the ^1H NMR spectrum at 3.83 ppm (quintet, *J* 6.4 Hz), shifted downfield by the neighbouring oxygen atom. The corresponding molecular ion (M^+ 358) was observed by EI-MS and the purity was further verified by elemental analysis. The cyclization with potassium *tert*-butoxide was repeated in

THF as solvent to avoid formation of unwanted *oxa*-Michael addition products, but also ended in failure.

Strong bases such as LiOBu t , LiHMDS and NaH were examined next (Table 1). Gratifyingly, formation of the corresponding IMAMR product could be observed under these conditions in modest to good yields (entries 1–5). Interestingly, for the reaction facilitated by NaH, the conversion was never greater than 50 % (entries 1–3). Different work up procedures were adopted, including quenching with NaHCO $_3$, NH $_4$ Cl, and HCl, but conversions were found to be independent of the proton source. Although $t\text{BuOLi}$ was the weakest base examined (entry 5), it outperformed NaH significantly and was comparable to LiHMDS (entry 4). However, LiHMDS could be employed at lower reaction temperatures to convert **13** cleanly to **15**. The ^1H NMR spectroscopy signals in the aromatic region (6.0 to 8.0 ppm) were typical of an *ortho*-disubstituted aryl group. The pendent ester was confirmed by the presence of carbonyl resonance in the ^{13}C NMR spectrum at 172.5 ppm. Finally, the methine *CH* resonance, which is shifted upfield by the neighbouring nitrogen, was assigned by a HMQC-dept135 correlation experiment.

Table 1 Screening of bases for the IMAMR.^a



Entry	Base (quenching agent)	Equivalent	$\sim\text{pK}_a$ (of conj.acid)	Temp/ $^\circ\text{C}$	Conversion (Yield)/% ^b
1	NaH (NaHCO $_3$ (aq))	1.3	37	70	50 (38)
2	NaH (NH $_4$ Cl(aq))	1.3	37	70	50 (31)
3	NaH (0.1 M HCl)	1.3	37	70	50 (36)
4	LiHMDS (NH $_4$ Cl(aq))	10	30	-10	100 (78)
5	$t\text{BuOLi}$ (NH $_4$ Cl(aq))	10	19	70	100 (81)

^a Reaction conditions: NaH (1.3 equiv) or LiHMDS (10 equiv) or $t\text{BuOLi}$ (10 equiv), substrate **13** (0.3 mmol), THF (3 mL), 1–4 h, N $_2$ atmosphere.

^b Conversions were determined by integration of the ^1H NMR spectrum. Values in brackets correspond to isolated yields after column chromatography.

4. Conclusion

In summary, (*E*)-ethyl 7-oxohept-2-enoate cyclized spontaneously during acidic workup to provide ethyl 2-(1-phenylpiperidin-2-yl)acetate whereas, a 6-(arylamino)hex-2-enoate could only be cyclized to the corresponding *N*-phenylpyrrolidin-2-yl heterocycle in synthetically useful yields with the aid of a stoichiometric amount of base. The procedure leading to the pyrrolidin-2-yl structures is simple, clean, inexpensive and efficient, providing the target heterocyclic ring systems in 4 steps. The yields for the ring closure are at present only modest, and we are therefore continuing our work to improve the key C-N bond ring forming step and currently exploring the application of these products to the synthesis of polycyclic heterocyclic systems.

5. Experimental

All commercial reagents were used as received. Column chromatography was performed using silica gel 200–400 Mesh. TLC analysis were performed using silica gel plates, using ultraviolet light (254 nm) or vanillin solution for visualization. Melting points are uncorrected.

IR spectra were recorded using samples that were prepared as either a liquid film between NaCl plates, or pressed in to KBr discs. For NMR spectroscopy data, the chemical shifts are reported in ppm referenced to residual protons and ^{13}C signals in deuterated chloroform. The coupling constants (*J*) are expressed in Hertz (Hz).

Tetrahydropyran-2-ol. In a 3-necked 250 mL round-bottom flask equipped with magnetic stir bar, 3,4-dihydro-2H-pyran (8.3 g, 100 mmol) was added drop-wise to a solution of 2 M HCl (20 mL) at 0 °C over 30 min. The mixture was then allowed to warm to room temperature, stirred for an additional 1 h, neutralized with saturated NaHCO_3 , and then extracted with DCM (2 × 20 mL). The combined extracts were dried over Na_2SO_4 , filtered, concentrated in vacuo and the residue was used without further purification (6.3 g, 94 %). Transparent oil. Spectroscopic data are in accordance with literature values.³¹

(*E*)-Ethyl 7-hydroxyhept-2-enoate (7). Tetrahydropyran-2-ol (1 g, 9.8 mmol), Triethylphosphonoacetate (4.4 g, 12.3 mmol), and DCM (30 mL) were mixed together in a dry 100 mL round-bottom flask equipped with magnetic stir bar under nitrogen atmosphere. The solution was stirred at room temperature for 18 hours, and then it was concentrated. The resulting solid was taken up in *n*-hexane (40 mL), and the suspension was stirred for 0.5 hours. The solid was filtered off and washed with *n*-hexane. The filtrate was concentrated and purified by column chromatography to afford the unsaturated ester **7** (677 mg, 80 %). Transparent oil; $R_f = 0.3$ (Hexanes/ EtOAc, 3:2); ν_{max} (thin film, cm^{-1}): 3365, 2920, 1711, 1655, 1457, 1369, 1304, 1192, 1043, 982, 863, 808, 735; δH (400 MHz, CDCl_3): 6.98 (1H, dt, *J* 7.2, 15.6), 5.85 (1H, dt, *J* 1.6, 15.6), 4.21 (2H, q, *J* 6.8, OCH_2), 3.69 (2H, t, *J* 6.0), 2.28 (2H, q, *J* 7.2), 1.47–1.62 (4H, m), 1.31 (3H, t, *J* 6.8, OCH_2CH_3); δC (100 MHz, CDCl_3): 166.7 (C=O), 148.5, 121.6, 62.5, 60.2 (OCH_2), 32.0, 31.8, 25.3, 14.3 (OCH_2CH_3); *m/z* (EI): 172 (M^+ , 2 %), 154 (4 %), 126 (70 %), 81 (100 %), 68 (40 %), 55 (50 %). NMR spectroscopy data are in accordance with literature values.³⁰

(*E*)-Ethyl 6-hydroxyhex-2-enoate (8). The previous procedure was modified for the synthesis of **7**. Triethylphosphonoacetate (7.7 g, 22.2 mmol) and 2-hydroxytetrahydrofuran (1.5 g, 17.1 mmol), were refluxed in anhydrous toluene for 18 hours. Upon completion the product was isolated column chromatography by afford

8 (2.0 g, 74 %). Transparent oil; $R_f = 0.2$ (Hexanes/ EtOAc, 3:2); ν_{max} (thin film, cm^{-1}): 3384, 2939, 1710, 1656, 1445, 1369, 1274, 1197, 1097, 1044, 981, 917, 711; δH (400 MHz, CDCl_3): 6.97 (1H, dt, *J* 7.2, 15.6), 5.88 (1H, dt, *J* 1.6, 15.6), 4.23 (2H, q, *J* 6.8, OCH_2), 3.70 (2H, t, *J* 6.0), 2.34 (2H, q, *J* 7.2), 1.74–1.79 (3H, br m, H-5, OH), 1.32 (3H, t, *J* 6.8, OCH_2CH_3); δC (100 MHz, CDCl_3): 166.7 (C=O), 148.5, 121.8, 61.9, 60.2 (OCH_2), 30.9, 28.5, 14.3 (OCH_2CH_3); *m/z* (EI): 158 (M^+ , 5 %), 127 (55 %), 112 (98 %), 84 (50 %), 67 (100 %), 55 (65 %). NMR spectroscopy data are in accordance with literature values.²⁹

(*E*)-Ethyl 6-oxohex-2-enoate (9). To a solution of **8** (200 mg, 1.2 mmol) in 50 mL of dry DCM was added PCC (375 mg, 1.7 mmol). The resultant reaction mixture was stirred at room temperature for 3 hours and dried over MgSO_4 . The filtrate was concentrated to dryness under reduced pressure and the residual material was purified by column chromatography to give the aldehyde **9** (157 mg, 74 %). Transparent oil; $R_f = 0.2$ (DCM); ν_{max} (thin film, cm^{-1}): 2982, 2938, 1720, 1654, 1312, 1268, 1193, 1043, 984, 852; δH (400 MHz, CDCl_3): 9.78 (1H, s, CHO), 6.95 (1H, dt, *J* 7.2, 15.6), 5.85 (1H, dt, *J* 1.6, 15.6), 4.21 (2H, q, *J* 6.8, OCH_2), 2.51 (2H, t, *J* 7.2), 2.28 (2H, q, *J* 7.2), 1.84 (2H, quintet, *J* 7.2), 1.30 (3H, t, *J* 6.8, OCH_2CH_3); δC (100 MHz, CDCl_3): 201.6 (CHO), 166.4 (C=O), 147.5, 122.3, 60.2, 43.2, 31.2, 20.3, 14.2 (OCH_2CH_3); *m/z* (EI): 170 (M^+ , 1 < N > %), 127 (40 %), 124 (60 %), 114 (90 %), 99 (85 %), 81 (100 %), 68 (70 %). NMR spectroscopy data are in accordance with literature values.³²

(*E*)-Ethyl 7-oxohept-2-enoate (10). The previous procedure was repeated using **7** (450 mg, 2.8 mmol) and PCC (918 mg, 4.3 mmol) to give the aldehyde **10** (324 mg, 80 %). Transparent oil; $R_f = 0.2$ (DCM); ν_{max} (thin film, cm^{-1}): 3423, 2983, 2729, 1719, 1654, 1368, 1272, 1163, 1097, 981; δH (400 MHz, CDCl_3): 9.79 (1H, s, CHO), 6.96 (1H, dt, *J* 7.2, 15.6), 5.86 (1H, dt, *J* 1.6, 15.6), 4.20 (2H, q, *J* 6.8, OCH_2), 2.66 (2H, t, *J* 7.2), 2.56 (2H, q, *J* 7.2), 1.30 (3H, t, *J* 6.8, OCH_2CH_3); δC (100 MHz, CDCl_3): 200.4 (CHO), 166.3 (C=O), 146.3, 122.5, 60.4 (OCH_2), 41.8, 24.4, 14.2 (OCH_2CH_3); *m/z* (EI): 156 (M^+ , 1 < N > %), 155 (45 %), 141 (40 %), 113 (75 %), 108 (65 %), 94 (100 %), 67 (55 %). NMR spectroscopy data are in accordance with literature values.³³

Ethyl 2-(1-phenylpiperidin-2-yl)acetate (11). In a two-neck 150 mL round bottom flask, equipped with stir bar and reflux condenser, aniline (852 μCL , 8.1 mmol), aldehyde **10** (500 mg, 2.7 mmol) and magnesium sulphate (2 g) were dissolved in THF (65 mL), and the reaction mixture was stirred at room temperature for 0.5 h. sodium triacetoxyborohydride (3.0 mmol) was added, and the mixture was heated to 65 °C for 20 h. Upon completion, solvent was reduced under reduced pressure, and the residue dissolved in 1 M HCl (30 mL) and then carefully neutralized using aqueous saturated sodium bicarbonate solution, and finally extracted with EtOAc (4 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 , and the solvent was removed under reduced pressure to yield **11** (426 mg, 64 %). Transparent oil; $R_f = 0.3$ (Hexanes/Diethyl ether, 4:1); ν_{max} (thin film, cm^{-1}): 2979, 2936, 2862, 2825, 2254, 1703, 1598, 1498, 1370, 1292, 1252, 1177, 1112, 1034, 991, 918, 753, 733, 693, 647; δH (400 MHz, CDCl_3): 7.29 (2H, t, *J* 8.0, H_{meta}), 6.99 (2H, d, *J* 8.0, H_{ortho}), 6.86 (1H, t, *J* 8.0, H_{para}), 4.40–4.42 (1H, m), 4.09 (2H, q, *J* 7.2, OCH_2), 3.40 (1H, d, *J* 12.0, H-6_{endo}), 2.97 (1H, t, *J* 12.0, H-6_{exo}), 2.60 (1H, dd, *J* 9.6, 14.8, CH_2), 2.51 (1H, dd, *J* 4.8, 14.8, CH_2), 1.89–1.78 (6H, m), 1.25 (3H, t, *J* 7.2, OCH_2CH_3); δC (100 MHz, CDCl_3): 172.5 (C=O), 150.3 (C_{ipso}), 129.2 (C_{meta}), 119.2 (C_{para}), 117.1 (C_{ortho}), 60.4 (OCH_2), 53.2, 44.0, 32.8, 28.8, 25.5, 19.2, 14.2 (OCH_2CH_3); *m/z* (EI): 247 (M^+ ,

20 %), 160 (100 %), 132 (10 %), 104 (15 %), 77 (20 %). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84 %; H, 8.56 %; N, 5.66 %. Found: C, 72.75 %; H, 8.47 %; N, 5.56 %.

(E)-Ethyl 7-(phenylamino)hept-2-enoate (12). This compound was isolated from the previously described reaction. **12** (12 %). Transparent oil; $R_f = 0.1$ (Hexanes/Et₂O, 4:1); ν_{max} (thin film, cm⁻¹): 3394, 2982, 2937, 2861, 2252, 1711, 1654, 1603, 1504, 1477, 1369, 1314, 1268, 1181, 1041, 983, 910, 735, 693, 648; δH (400 MHz, CDCl₃): 7.23 (2H, t, J 7.4), 7.03 (1H, dt, J 6.8, 15.6, CH₂CH=CH), 6.75 (1H, t, J 7.4), 6.64 (2H, d, J 7.4), 5.89 (1H, dt, J 1.4, 15.6, CH₂CH=CH), 4.25 (2H, q, J 6.8, OCH₂), 3.63 (1H, br s, NH), 3.17 (2H, t, J 6.4, NHCH₂), 2.31 (2H, q, J 6.8, CH₂CH=CH), 1.66–1.68 (4H, m, NHCH₂CH₂CH₂), 1.34 (3H, t, J 6.8, OCH₂CH₃); δC (100 MHz, CDCl₃): 166.6 (C=O), 148.7 (CH₂CH=CH), 129.3, 121.7, 117.3, 112.7, 60.4 (OCH₂), 43.7 (NHCH₂), 31.9 (CH₂CH=CH) 29.1 (NHCH₂CH₂), 25.6 (CH₂CH₂CH=CH), 14.3 (OCH₂CH₃); m/z (EI): 247 (M⁺, 65 %), 202 (25 %), 132 (60 %), 106 (100 %), 93 (30 %), 77 (40 %). Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84 %; H, 8.56 %; N, 5.66 %. Found: C, 72.80 %; H, 8.59 %; N, 5.71 %.

(E)-Ethyl 6-(2-bromophenylamino)hex-2-enoate (13). The previously described procedure for compound **12** was repeated using 2-bromoaniline (504 mg, 2.9 mmol), aldehyde **9** (250 mg, 1.6 mmol) and sodium triacetoxyborohydride (2.4 mmol) to yield **13** (295 mg, 71 %). Transparent oil; $R_f = 0.2$ (Hexanes/DCM, 3:2); ν_{max} (thin film, cm⁻¹): 3404, 2933, 2861, 1720, 1656, 1593, 1511, 1459, 1317, 1273, 1201, 1169, 1042, 1018, 980, 743, 657; δH (400 MHz, CDCl₃): 7.44 (2H, t, J 8.0), 7.23 (1H, dt, J 1.2, 8.4), 7.03 (1H, dt, J 6.8, 15.6, CH₂CH=CH), 6.64 (2H, d, J 8.4), 6.61 (1H, dt, J 1.6, 8.0), 5.89 (1H, dt, J 1.6, 15.6, CH₂CH=CH), 4.30 (1H, br s, NH), 4.24 (2H, q, J 6.8, OCH₂), 3.23 (2H, br m, NHCH₂), 2.40 (2H, q, J 6.8, CH₂CH=CH), 1.90 (2H, quintet, J 7.2, NHCH₂CH₂), 1.33 (3H, t, J 6.8, OCH₂CH₃); δC (100 MHz, CDCl₃): 166.5 (C=O), 148.2 (CH₂CH=CH), 144.8, 132.4, 128.5, 122.2 (CH₂CH=CH), 117.7, 111.2, 109.7, 60.3 (OCH₂), 43.1 (NHCH₂), 29.6 (CH₂CH=CH) 27.6 (NHCH₂CH₂), 14.3 (OCH₂CH₃); m/z (EI): 312 (M⁺, 2 %), 311 (30 %), 187 (98 %), 184 (100 %), 105 (15 %), 77 (22 %). Anal. Calcd for $C_{14}H_{18}BrNO_2$: C, 53.86 %; H, 5.81 %; N, 4.49 %. Found: C, 55.91 %; H, 5.81 %; N, 4.62 %.

Ethyl 6-(2-bromophenylamino)-3-ethoxyhexanoate (14). An oven-dried Young's tube containing a stir bar, a rubber septum and KO^tBu (22 mg, 5 mol %) was purged and filled with nitrogen four times. Ethanol (3 mL) and the substrate **13** (307 mg, 0.98 mmol) were injected into the tube, which was sealed and refluxed for 22 hours. Upon completion, the reaction was quenched with saturated NH₄Cl (aq) (2 mL) and extracted with DCM (10 mL). The organic layer was dried over Na₂SO₄, concentrated under vacuum and the material purified by column chromatography to afford **14** (43 mg, 12 %). Pale yellow oil; $R_f = 0.2$ (Hexanes/DCM, 8:1); ν_{max} (thin film, cm⁻¹): 3214, 2813, 2382, 2315, 2255, 1748, 1708, 1593, 1502, 1456, 1373, 1319, 1201, 1164, 1090, 1020, 911, 733, 563; δH (400 MHz, CDCl₃): 7.44 (1H, d, J 7.6), 7.21 (1H, t, J 8.4), 6.65 (1H, d, J 8.4), 6.59 (1H, t, J 7.6), 4.32 (1H, br s, NH), 4.20 (2H, q, J 7.2, OCH₂), 3.83 (1H, quintet, J 6.4, CH), 3.54 (2H, m, CHOCH₂), 3.23 (2H, br m, ArCH₂), 2.63 (1H, dd, J 6.4, 15.2, CHCH₂), 2.46 (1H, dd, J 6.4, 15.2, CHCH₂), 1.65–1.83 (4H, m, ArCH₂CH₂CH₂), 1.30 (3H, t, J 7.2, OCH₂CH₃), 1.21 (3H, t, J 6.8, CHOCH₂CH₃); δC (100 MHz, CDCl₃): 171.6 (C=O), 144.7, 132.4, 128.5, 117.5, 111.2, 109.6, 75.8 (CH), 64.9 (OCH₂), 60.5 (CHOCH₂), 43.8 (NHCH₂), 39.9 (CHCH₂), 32.0 (CH₂CH), 25.0 (NHCH₂CH₂), 15.5 (OCH₂CH₃), 14.2 (CHOCH₂CH₃); m/z (EI): 358 (M⁺, 5 %), 357

(25 %), 328 (20 %), 282 (30 %), 186 (95 %), 184 (100 %), 157 (45 %), 111 (35 %). Anal. Calcd for $C_{16}H_{24}BrNO_3$: C, 53.64 %; H, 6.75 %; N, 3.91 %. Found: C, 53.71 %; H, 6.77 %; N, 3.88 %.

Ethyl 2-[1-(2-bromophenyl)pyrrolidin-2-yl]acetate (15). An oven-dried Young's tube containing a stir bar and a rubber septum was evacuated and backfilled with nitrogen four times. A solution of the substrate **13** (100 mg, 0.3 mmol in anhydrous THF (4 mL)) was placed into the tube *via* syringe and the solution was cooled to -10 °C using an ice-acetone bath. LiHMDS (1.0 M solution in THF, 256 μ CL, 256 mmol) was added to the solution, which was left to stir for 1 hour. The reaction was then allowed to warm to room temperature, the reaction was quenched with saturated NH₄Cl (aq) (2 mL) and extracted with DCM (10 mL). The organic mixture was dried over Na₂SO₄, concentrated under vacuum and the residue purified by column chromatography to afford the desired substituted *N*-pyrrolidine **15** (78 mg, 78 %). Pale yellow oil; $R_f = 0.1$ (Hexanes/DCM, 6:4); ν_{max} (thin film, cm⁻¹): 3376, 3060, 2975, 2874, 2360, 1897, 1731, 1585, 1474, 1436, 1372, 1314, 1245, 1193, 1155, 1101, 1026, 976, 849, 752, 720, 669; δH (400 MHz, CDCl₃): 7.56 (1H, d, J 8.4), 7.26 (1H, t, J 6.8), 7.08 (1H, d, J 8.4), 6.87 (1H, t, J 6.8), 4.22–4.25 (1H, m), 4.10 (2H, q, J 7.2), 3.88 (1H, dd, J 1.6, 6.4), 2.89–2.90 (1H, m), 2.59 (1H, dd, J 4.0, 15.2), 2.31–2.33 (1H, m), 2.23 (1H, dd, J 9.2, 15.2), 1.98–2.02 (1H, m), 1.88–1.91 (1H, m), 1.72–1.73 (1H, m), 1.24 (3H, t, J 7.2); δC (100 MHz, CDCl₃): 172.5 (C=O), 147.4, 134.2, 127.8, 123.2, 120.9, 118.5, 60.3, 56.4, 53.0, 38.8, 31.6, 23.8, 14.2; m/z (EI): 312 (M⁺, 5 %), 282 (10 %), 224 (100 %), 184 (25 %), 77 (20 %). Anal. Calcd for $C_{14}H_{18}BrNO_2$: C, 53.86 %; H, 5.81 %; N, 4.49 %. Found: C, 53.82 %; H, 5.71 %; N, 4.49 %.

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References

- 1 J.P. Michael, *J. Nat. Prod. Rep.*, 1996, **13**, 73.
- 2 M.G.P. Buffat, *Tetrahedron*, 2004, **60**, 1701.
- 3 C.L.J. Wang and M.A. Wuonola, *Org. Prep. Proced. Int.*, 1992, **24**, 585.
- 4 M. Pichon and B. Figadere, *Tetrahedron: Asymmetry*, 1996, **7**, 927.
- 5 A. Padwa, M.A. Brodney, B. Liu, K. Satake and T. Wu, *J. Org. Chem.*, 1999, **64**, 3595.
- 6 A.R. Katritzky, S. Rachwal and B. Rachwal, *Tetrahedron*, 1996, **52**, 15031.
- 7 A.R. Katritzky, C.W. Rees and E.F.V. Scrivenand, eds., *Comprehensive Heterocyclic Chemistry II: An Extended and Updated Review of the Literature, 1982–1995*, 2nd edn, Pergamon, Oxford, 1996.
- 8 C.J. Moody, *Advances in Nitrogen Heterocycles, Volume 3*, JAI Press, Connecticut, 1998.
- 9 J.L. Vicario, D. Badia, L. Carrillo, and Editors, *New Methods for the Asymmetric Synthesis of Nitrogen Heterocycles*, Research SignPost, Trivandrum, India, 2005.
- 10 W.W. Ried, *Chem. Ber.*, 1957, **90**, 815.
- 11 H.H. Stachel, *Archiv Der Pharmazie.*, 1963, **296**, 337.
- 12 V.V. Gogte, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 1977, **15B**, 769.
- 13 A.A. Nawojski, *Roczniki Chemii*, 1977, **51**, 2117.
- 14 J.J. Bozell and L.S. Hegedus, *J. Org. Chem.*, 1981, **46**, 2561.
- 15 J.L. Vicario, D. Badia, L. Carrillo, J. Etxebarria, E.Reyes and N. Ruiz, *Org. Prep. Proced. Int.*, 2005, **37**, 513.

- 16 P.L.P. Southwick, D.I. Sapper and L.A. Pursglove, *J. Am. Chem. Soc.*, 1950, **72**, 4940.
- 17 R.R. Baltrusis, *Chimija geterociklicheskich soedinenij*, 1981, 1097.
- 18 E.E., Carceller, J. Salas, M. Merlos, M. Giral, R. Ferrando, I. Escamilla, J. Ramis, J. Garcia-Rafanell and J. Forn, *J. Med. Chem.*, 2001, **44**, 3001.
- 19 H.H. MacPhillamy, R.L. Dziemian, R.A. Lucas and M.E. Kuehne, *J. Am. Chem. Soc.*, 1958, **80**, 2172.
- 20 J.J. Merchant, *Indian J. Chem.*, 1974, **12**, 351.
- 21 M.K. Chaudhuri, S. Hussain, M.L. Kantam and B. Neelima, *Tetrahedron Lett.*, 2005, **46**, 8329–8331.
- 22 T.C. Wabnitz, J.Q. Yu and J.B. Spencer, *Synlett*, 2003, 1070.
- 23 T.C. Wabnitz and J.B. Spencer, *Org. Lett.*, 2003, **5**, 2141.
- 24 For a review see: J. Seayad, A. Tillack, C.G. Hartung and M. Beller, *Adv. Synth. Catal.*, 2002, **344**, 795.
- 25 V. Khedkar, A. Tillack, C. Benisch, J.P. Melder and M. Beller, *J. Mol. Catal. A, Chemical*, 2005, **241**, 175.
- 26 M. Bandini, A. Eichholzer, M. Monari, F. Piccinelli and A. Umani-Ronchi, *Eur. J. Org. Chem.*, 2007, 2917.
- 27 M. Hirama, T. Iwakuma and S. Ito, *Chem. Commun.*, 1987, 1523.
- 28 S.H. Chen, B.C. Hong, C.F. Su and S. Sarshar, *Tetrahedron Lett.*, 2005, **46**, 8899.
- 28 T. Zheng, R.S. Narayan, J.M. Schomaker and B. Borhan, *J. Am. Chem. Soc.*, 2005, **127**, 6946.
- 30 G. Pandey, S. Hajra, M.K. Ghorai and K.R. Kumar, *J. Am. Chem. Soc.*, 1997, **119**, 8777.
- 31 S.H. Chen, B.C. Hong, C.F. Su and S. Sarshar, *Tetrahedron Lett.*, 2005, **46**, 8899.
- 32 T.R. Hoye, B.M. Eklov, J., Jeon and M. Khorroosi, *Org. Lett.*, 2006, **8**, 3383.
- 33 G. Pandey, S. Hajra and M.K. Ghorai, *J. Org. Chem.*, 1997, **62**, 5966.