SHORT PAPER

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Synthesis of phenyl and substituted phenyl 3-ethyl-2,3,5,9b-tetrahydro[1,3]oxazolo[2,3-a]isoindol-5-ones†

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Addition of various aryl magnesium bromides to (*R*) or (*S*)-2-(1-hydroxybutyl)phthalimide results in the formation of substituted (*R*) or (*S*)–3-hydroxy-2(1-hydroxybutyl)isoindol-1-ones which are subsequently cyclised under highly acidic conditions to give the title compounds in moderate yields.

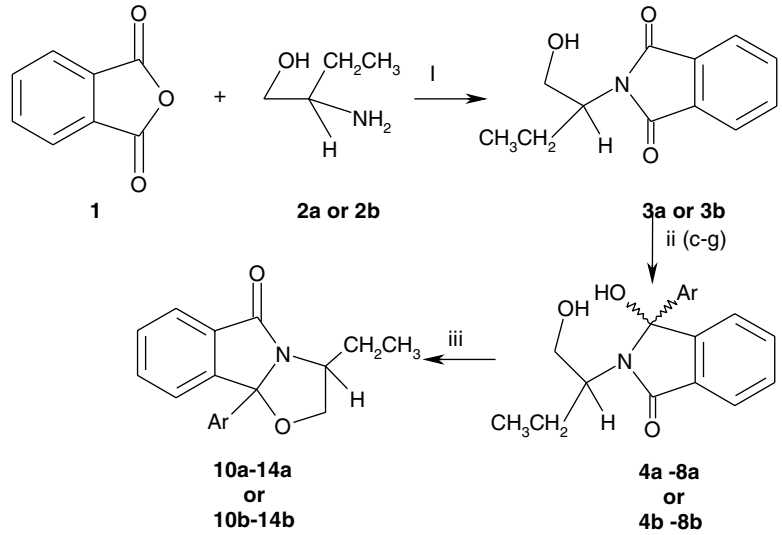
Keywords: amino butanol, chiral synthon, isoindolinones

Oxazolo[2,3-a]isoindol-5-one derivatives exhibit anti-convulsant and anti-inflammatory activities.[1] The chemistry and reactivity of isoindolinone ring system is an area of interest because of its biological activity.[2] Recently Allin and coworkers[3] have reported a new synthesis of non-racemic isoindolinone targets through application of oxazolo-[2,3-a]isoindolinones as N-acyl iminium ion precursors in reactions with carbon and hydride nucleophiles. We had earlier reported the formation of a novel 10 membered chiral ring system[4] while attempting to synthesise oxazolo-[2,3-a]isoindol-5(9bH)-one using (*R*) or (*S*)-2-amino-1-butanol via Meyers methodology[5] involving reduction of the imide and cyclisation using trifluoro acetic acid. The phenyl group was introduced by the addition of phenyl magnesium bromide (**c**) to (*R*) or (*S*)-2-(1-hydroxy)phthalimides **3a** or **3b**. These were derived from phthalic anhydride **1** and (*R*)-(-)-2-amino-1-butanol **2a** or (*S*)-(+)-2-amino-1-butanol **2b**. The resulting dihydroxy compounds **4a** or **4b** were not isolated, but were directly subjected to acid-catalysed cyclisation to furnish the 9b-phenyl substituted oxazolo[2,3a] isoindolinones **10a** or **10b** in 40-50% yields. In a similar fashion the addition of *p*-fluoro(**d**), *p*-chloro(**e**), *p*-methoxy(**f**) and *p*-methyl(**g**) substituted phenyl magnesium bromides furnished the corresponding 9b-substituted-phenyl substituted oxazolo[2,3a] isoindolinones **11a–14a** or **11b–14b** respectively (Scheme 1).

Table 1 Preparation of tricyclic lactams through addition of different Grignard reagents and subsequent cyclisation

Substrate	Grignard reagent	Ar	Product
3a	c	Ph	**10a**
3b	c	Ph	**10b**
3a	d	4-FPh	**11a**
3b	d	4-FPh	**11b**
3a	e	4-ClPh	**12a**
3b	e	4-ClPh	**12b**
3a	f	4-OCH_3	**13a**
3b	f	4-OCH_3	**13b**
3a	g	4-CH_3	**14a**
3b	g	4-CH_3	**14b**

Compound **10b** was subjected to a single crystal X-ray diffraction analysis[6] and its structure was solved and refined by SHELX 97 program[7] (Fig. 1). The absolute configuration of the phenyl substituted oxazolo[2,3-a]isoindolin-5-one was found to be (3*S*, 9b*R*).



Scheme 1 Reagents and conditions (i) Neat, 140°C (ii) **c-** C_6H_5MgBr, **d-** *p*-FC_6H_4MgBr, **e-***p*-ClC_6H_4MgBr, **f-** *p*-$OCH_3C_6H_4MgBr$, **g-***p*-CH_3 C_6H_4MgBr, 3 hours, N_2 atmos., R.T. (iii) CF_3COOH, CH_2Cl_2, 2–3 hours.

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† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

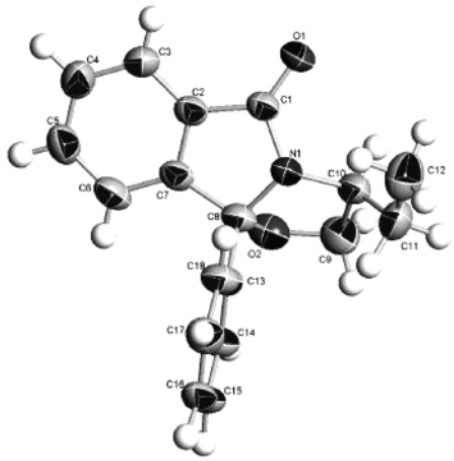
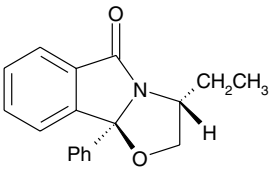
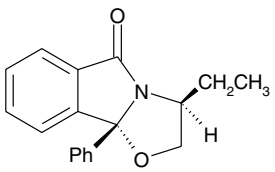


Fig. 1 ORTEP plot of compound **10b**. Ellipsoids drawn at 50% probability.

The structures of **10a** and **10b** can be given as follows:



10a



10b

Cyclisation takes place via the usual N-acyl iminium ion species. The N-acyl iminium ion being planar, attack of the hydroxyl group can take place from either of the two possible sides, but in this case attack takes place on one of the sides. This can be attributed to the fact that the folded shape of the fused 5,5-bicyclic system requires both the 3-ethyl and 9b-phenyl substituents to be *cis* on the *exo* face. The Grignard reactions proceeded with low yields. However, they may provide a valuable tool for introducing a number of substituted phenyl groups into the tricyclic lactams.

Experimental

Reagent chemicals were purchased from Lancaster Synthesis Ltd and Aldrich Chemical Co. Ltd. and were purified when necessary before use. Solvents were distilled and dried before use. Tetrahydrofuran (THF) for Grignard reactions was distilled over sodium wire and stored over sodium wire. Dichloromethane (MDC) was dried, distilled and stored over 4A° molecular sieves before use. Column chromatography was carried out using silica gel (60–120 mesh). Thin layer chromatography (TLC) was carried out using silica gel (75µm). Yields are quoted for isolated, purified and dried products. Infrared spectra for the solids were recorded in the range 4000–600cm^{-1} using Perkin-Elmer FT-IR16PC spectrometer with KBr pellet. Proton NMR was recorded using Bruker 200 MHz spectrometer. Elemental analysis was carried out on a Perkin-Elmer C, H, and N elemental analyzer. Specific rotations were measured using JASCO P-1030 polarimeter.

Synthesis of phenyl and substituted phenyl oxazolo[2,3-a] isoindolinones (general method): Grignard reagents were prepared by the usual procedure using the corresponding aryl bromides and magnesium in THF under nitrogen atmosphere.

(*R*) or (*S*)- 2-(1-Hydroxybutyl)phthalimide **3a** or **3b** (2.0g, 9.13 mmol) dissolved in dry THF is taken in two neck round bottom flask flushed with nitrogen. Grignard reagent **c–g** (3 equivalents) was added within 4–5 minutes. Then the solution was stirred for 3 hours at room temperature. A saturated solution of ammonium chloride was added and the solution extracted with dichloromethane. Removal of the solvent gave the crude product, which was dissolved in dry dichloromethane and added in portions to a stirred solution of trifluoroacetic acid (10 equivalents) in dry dichloromethane. The solution was stirred at room temperature for 2–3 hours. A saturated solution of sodium bicarbonate was added. The dichloromethane extract was washed with brine and dried over sodium sulfate. Dichloromethane was then distilled off to obtain a crude product which was purified using column chromatography with petroleum ether:ethylacetate (80:20) to obtain the corresponding cyclic products **10a**–**14a** or **10b**–**14b** in pure form.

10a: (45%), $[\alpha]_D^{20}$ 261.97° (c 1.0, methanol); [Found: C, 77.53; H, 6.12; N, 4.93. $C_{18}H_{17}O_2N$ requires C, 77.41; H, 6.093; N, 5.017%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, –CH_2–C$\underline{H}_3$), 1.4 (2H, m, –CH–C$\underline{H}_2$–CH_3), 3.8 (1H, t, *J* 8.0, –CH–C$\underline{H}_2$–O), 4.2 (1H, q, *J* 8.0, –CH_2–C$\underline{H}$–CH_2–), 4.6 (1H, t, *J* 8.0, –CH–C$\underline{H}_2$–O); 7.1–7.8 (9H, m, Ar–$\underline{H}$); ^{13}C NMR δ_C ($CDCl_3$, 50.33MHz) 175.27(C), {147.77, 139.59, 133.80, 131.82, 130.69, 129.37, 129.26, 126.32, 124.98, 124.06}(Ar–C), 101.36(C), 76.74(CH), 58.13(CH_2), 28.11(CH_2), 11.86(CH_3); ν_{max}/cm^{-1}(KBr pellet) 1716, 1610, 1450, 1320, 1240, 750. **10b**: (47%), $[\alpha]_D^{20}$ –263.72° (c 1.0, methanol); [Found: C, 77.55; H, 6.09; N, 4.92. $C_{18}H_{17}O_2N$ requires C, 77.41; H, 6.093; N, 5.017 %]; δ_H (200MHz, $CDCl_3$) 1.0 (3H, t, –CH_2–C$\underline{H}_3$), 1.4 (2H, m, –CH_2–C$\underline{H}_2$–CH_3), 3.8 (1H, t, *J* 8.0, –CH–C$\underline{H}_2$–O), 4.2 (1H, q, *J* 8.0, CH_2–C$\underline{H}$–CH_2), 4.6 (1H, t, *J* 8.0 Hz, –CH–C$\underline{H}_2$–O), 7.1–7.8 (9H, m, Ar–$\underline{H}$); ^{13}C NMR δ_C ($CDCl_3$, 50.33MHz) 175.27(C), {147.77, 139.59, 133.80, 131.82, 130.69, 129.37, 126.32, 124.98, 124.06}(Ar–C), 101.36(C), 76.74(CH), 58.13(CH_2), 28.11(CH_2), 11.86(CH_3); ν_{max}\cm^{-1}(KBr pellet) 1716, 1610, 1450, 1320, 1240, 750. **11a**: (40%), $[\alpha]_D^{20}$ 264.8° (c 1.0, $CHCl_3$); [Found: C, 72.51; H, 5.40; N, 4.69. $C_{18}H_{16}O_2NF$ requires C, 72.72; H, 5.38; N, 4.71%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, –CH_2–C$\underline{H}_3$), 1.4 (2H, m, –CH–C$\underline{H}_2$–CH_3), 3.8 (1H, t, *J* 7.0–8.0, –CH–C$\underline{H}_2$–O), 4.2 (1H, q, *J* 8.0, –CH_2–C$\underline{H}$–CH_2–), 4.6 (1H, t, *J* 7.0–8.0, –CH–C$\underline{H}_2$–O), 7.1–7.8 (8H, m, Ar–$\underline{H}$); ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.16(C), {161.09, 147.59, 135.50, 134.27, 133.58, 131.63, 130.58, 128.28, 125.017, 123.91}(Ar–C), 100.98(C), 76.69(CH), 58.14(CH_2), 28.08(CH_2), 11.78(CH_3); ν_{max}/cm^{-1}(Nujol mull) 1737, 1600, 1463, 1377, 722 .**11b**: (41%), $[\alpha]_D^{20}$ –242.19° (c 1.0, $CHCl_3$); [Found: C, 72.65; H, 5.30; N, 4.70. $C_{18}H_{16}O_2NF$ requires C, 72.72; H, 5.38; N, 4.71%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, –CH_2–C$\underline{H}_3$), 1.4 (2H, m, –CH–C$\underline{H}_2$–CH_3), 3.8 (1H, t, *J* 7.0–8.0, –CH–C$\underline{H}_2$–O), 4.6 (1H, t, *J* 7.0–8.0, –CH–C$\underline{H}_2$–O), 4.2 (1H, q, *J* 8.0, –CH_2–C$\underline{H}$–CH_2–), 7.1–7.8 (8H, m, Ar–$\underline{H}$) ; ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.16(C), {161.09, 147.59, 135.50, 134.27, 133.58, 131.63, 130.58, 128.28, 125.017, 123.91}(Ar–C), 100.98(C), 76.69(CH), 58.14(CH_2), 28.08(CH_2), 11.78(CH_3); ν_{max}/cm^{-1}(Nujol mull) 1737, 1600, 1463, 1377, 722. **12a**: (43%), $[\alpha]_D^{20}$ 266.64° (c 1.0, $CHCl_3$); [Found: C, 68.90; H, 5.03; N, 4.41. $C_{18}H_{16}O_2NCl$ requires C, 68.89; H, 5.10; N, 4.46%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, –CH_2–C$\underline{H}_3$), 1.4 (2H, m, –CH–C$\underline{H}_2$–CH_3), 3.8 (1H, t, *J* 7.0–8.0, – CH–C$\underline{H}_2$–O), 4.2 (1H, q, *J* 8.0, –CH_2–C$\underline{H}$–CH_2–), 4.6 (1H, t, *J*7.0–8.0, –CH–C$\underline{H}_2$–O), 7.1–7.8 (8H, m, Ar–$\underline{H}$) ; ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.10(C), {150.11, 147.35, 135.24, 133.9, 131.66, 130.86, 129.61, 127.81, 125.06, 123.93}(Ar–C), 100.90(C), 76.72(CH), 58.15(CH_2), 28.10(CH_2), 11.79(CH_3); ν_{max}/cm^{-1}(Nujol mull) 1736, 1599, 1462, 1376, 722.**12b**: (41%), $[\alpha]_D^{20}$ –250.22° (c 1.0, $CHCl_3$); [Found: C, 68.70; H, 5.05; N, 4.42. $C_{18}H_{16}O_2NCl$ requires C, 68.89; H, 5.10; N, 4.46%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, –CH_2–C$\underline{H}_3$), 1.4 (2H, m, –CH–C$\underline{H}_2$–CH_3), 3.8 (1H, t, *J*7.0–8.0, –CH–C$\underline{H}_2$–O), 4.2 (1H, q, *J* 8.0, –CH_2–C$\underline{H}$–CH_2–), 4.6 (1H, t, *J*7.0–8.0, –CH–C$\underline{H}_2$–O), 7.1–7.8 (8H, m, Ar–$\underline{H}$); ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.10(C), {150.11, 147.35, 135.24, 133.9, 131.66, 130.86, 129.61, 127.81, 125.06, 123.93}(Ar–C), 100.90(C), 76.72(CH), 58.15(CH_2), 28.10(CH_2), 11.79(CH_3); ν_{max}/cm^{-1}(Nujol mull) 1736, 1599, 1462, 1376, 722 .**13a**: (52%), $[\alpha]_D^{20}$ 207.14° (c 1.0, $CHCl_3$); [Found: C, 73.85; H, 6.04; N, 4.48. $C_{19}H_{19}O_3N$ requires C, 73.78; H, 6.14; N, 4.53%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, –CH_2–C$\underline{H}_3$), 1.4 (2H, m, –CH–C$\underline{H}_2$–CH_3), 3.8 (1H, t, *J* 7.0–8.0, –CH–C$\underline{H}_2$–O), 3.81(3H, s, –OCH_3) 4.2 (1H, q, *J* 8.0, –CH_2–C$\underline{H}$–CH_2–), 4.6 (1H, t, *J* 7.0–8.0, –CH–C$\underline{H}_2$–O), 7.1–7.8 (8H, m, Ar–$\underline{H}$) ; ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.15(C), {160.43, 147.89, 133.67, 131.62, 131.29, 130.47, 127.52, 124.79, 123.85, 114.63}(Ar–C), 101.18(C), 76.58(CH), 57.99(CH_2), 55.81(CH_3), 28.01(CH_2), 11.79(CH_3); ν_{max}/cm^{-1}(Nujol mull) 1732.47, 1611, 1510, 1459, 1377, 722. **13b**: (55%), $[\alpha]_D^{20}$ –212.99° (c 1.0, $CHCl_3$); [Found: C, 73.71; H, 6.10; N, 4.52. $C_{19}H_{19}O_3N$ requires C, 73.78; H, 6.14; N, 4.53%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, –CH_2–C$\underline{H}_3$), 1.4 (2H, m, –CH–C$\underline{H}_2$–CH_3), 3.8 (1H, t, *J* 7.0–8.0, –CH–C$\underline{H}_2$–O), 3.81(3H, s, –OCH_3) 4.2 (1H, q, *J* 8.0, –CH_2–C$\underline{H}$–CH_2–), 4.6 (1H, t, *J* 7.0–8.0, –CH–C$\underline{H}_2$–O), 7.1–7.8 (8H, m, Ar–$\underline{H}$) ; ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.15(C), {160.43, 147.89, 133.67, 131.62, 131.29, 130.47, 127.52, 124.79, 123.85, 114.63}(Ar–C), 101.18(C), 76.58(CH), 57.99(CH_2), 55.81(CH_3), 28.01(CH_2), 11.79(CH_3); ν_{max}/cm^{-1}(Nujol mull) 1732.47, 1611, 1510, 1459, 1377, 722. **14a**: (48%), $[\alpha]_D^{20}$ 221.49°

(c 1.0, $CHCl_3$); [Found: C, 77.76; H, 6.16; N, 4.69. $C_{19}H_{19}O_2N$ requires C, 77.81; H, 6.48; N, 4.78%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, –CH_2–C<u>H</u>$_3$), 1.4 (2H, m, –CH–C<u>H</u>$_2$–CH_3), 2.3(3H, s, –CH_3), 3.8 (1H, t, *J*7.0–8.0, –CH–C<u>H</u>$_2$–O), 4.2 (1H, q, *J* 8.0, –CH_2–C<u>H</u>–CH_2–), 4.6 (1H, t, *J* 7.0–8.0, –CH–C<u>H</u>$_2$–O), 7.1–7.8 (8H, m, Ar–<u>H</u>); ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.10(C), {147.76, 138.90, 136.39, 133.61, 131.65, 130.44, 129.94, 126.09, 124.74, 123.86}(Ar–C), 101.23(C), 76.54(CH), 57.94(CH_2), 27.97(CH_2), 21.67(CH_3), 11.75(CH_3); ν_{max}/cm^{-1}(Nujol mull) 1732.65. **14b**: (45%), $[\alpha]_D^{20}$ –215.69° (c 1.0, $CHCl_3$); [Found: C, 77.73; H, 6.39; N, 4.65. $C_{19}H_{19}O_2N$ requires C, 77.81; H, 6.48; N, 4.78%]; δ_H (200 MHz, $CDCl_3$) 1.0 (3H, t, –CH_2–C<u>H</u>$_3$), 1.4 (2H, m, –CH–C<u>H</u>$_2$–CH_3), 2.3(3H, s, –CH_3), 3.8 (1H, t, *J* 7.0–8.0, –CH–C<u>H</u>$_2$–O), 4.2 (1H, q, *J* 8.0, –CH_2–C<u>H</u>–CH_2–), 4.6 (1H, t, *J* 7.0–8.0, –CH–C<u>H</u>$_2$–O), 7.1–7.8 (8H, m, Ar–<u>H</u>) ; ^{13}C NMR δ_C ($CDCl_3$, 50.33 MHz) 175.10(C), {147.76, 138.90, 136.39, 133.61, 131.65, 130.44, 129.94, 126.09, 124.74, 123.86}(Ar–C), 101.23(C), 76.54(CH), 57.94(CH_2), 27.97(CH_2), 21.67(CH_3), 11.75(CH_3); ν_{max}/cm^{-1}(Nujol mull)1732, 1462, 1377, 722 .

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References

1 (a) W.J. Houlihan, U.S. Patent 3, 334, 113 and divisions thereof; *Chem. Abstr.* 1968, **68**, 58900; (b) T.S. Sulkowski, U.S.Patent 3, 336, 306; *Chem. Abstr.* 1968, **68**, 69007.

2 W. Schafer, W.G. Friebe, H. Leinert, A. Mertens, T. Poll, W. Vondersaal, H. Zilch, B. Nber and N.L. Ziegler, *J. Med. Chem.* 1993**, 36**, 726.

3 S.M. Allin, C.J. Northfield, M.I. Page and A.M.Z. Slawin, *J. Chem. Soc., Perkin Trans1*. 2000, 1715-1721.

4 G. Bijukumar, A.C. Shah and T. Pilati, *Tetrahedron Lett*. 1997, **38**, 3297.

5 A.I. Meyers, B.A. Lefker, J.J Sowin and L.J. Westrum, *J. Org Chem*. 1989, **54**, 4243.

6 Single crystals of compound **10b** were grown by slow evaporation of the solution in ethyl acetate / petroleum ether solvent mixture. Transparent crystal of approximate size 0.237 x 0.461 x 0.556 mm, was used for data collection on *Bruker SMART APEX* CCD diffractometer using Mo K_α radiation with fine focus tube with 50kV and 30mA. 2θ range = 4.04 to 57.7 °, completeness to 2θ of 57.7 ° is 90.7%. SADABS correction applied. 2 × ($C_{18}H_{17}NO_2$), *M* = 558.65. Crystals belong to monoclinic, space group P 2_1, *a* = 8.338 (2), *b* = 20121 (4), *c* = 9.416 (2) Å, β = 109.440 (3) °, *V* = 1489.7(5) Å^3, *Z* = 2, D_c = 1.245 mg m^{-3}, μ (Mo–K_α) = 0.081 mm^{-1}, *T* = 293(2) K, 8976 reflections measured, 5894 unique [I>2σ(I)], R value 0.0448, wR_2 = 0.1163 (all data R = 0.0528, wR_2 = 0.1208). All the data were corrected for Lorentzian, polarisation and absorption effects. SHELX-97 (ShelxTL) was used for structure solution and full matrix least squares refinement on F^2.

7 G. M. Sheldrick, SHELX-97 program for crystal structure solution and refinement, University of Gottingen, Germany, 1997.