Effect of A-Strain on a Synthesis of *cis*-Fused 4a-Aryloctahydro-1*H*-cyclopenta[*c*]pyridine Derivatives through Tandem Radical Cyclisation of an α-Acylamino–Polyene System

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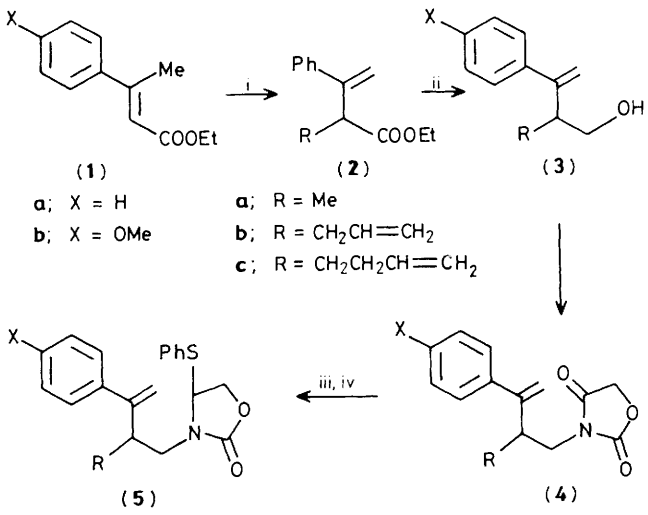
An efficient synthesis of the *cis*-fused 4a-aryloctahydro-1*H*-cyclopenta[*c*]pyridine ring system, an analogue of 4a-aryldecahydroisoquinoline, was achieved through a tandem radical approach by cyclisation of free radical–polyene species.

The construction of bicyclic systems *via* free radical cyclisation at an unsaturated component is becoming important.[1] In these reactions, α-acylamino radicals have been used as versatile synthetic entries into *N*-heterocycles.[2] Recently, tandem radical cyclisation by the use of free radical–polyolefinic systems was applied to the synthesis of condensed carbocyclic systems.[3] Our interest in a polyene cyclisation strategy[4] for synthesis of potentially biologically active aza-polycyclic compounds led us to investigate a synthetic approach to the 4a-aryloctahydro-1*H*-cyclopenta[*c*]pyridine ring system. This is of interest from both synthetic and pharmacological points of view, since it is an analogue of 4a-aryldecahydroisoquinolines, which are significant as simple versions of morphine-based molecules.[5] Our strategy is based on a tandem radical cyclisation using polyene–α-amino radical species. The results of our studies are described herein. 4-Phenylthio-oxazolidin-2-ones (**5a**—**d**), used for the generation of radical species, were prepared as outlined in Scheme 1. Reduction of esters (**2a**—**c**), obtained by α-alkylation of (**1a**), with $LiAlH_4$ gave the corresponding alcohols (**3a**—**c**),† respectively. Condensation of (**3a**—**c**) and (**3d**)[4c] derived from (**1b**) with oxazolidine-2,4-dione by Mitsunobu's method[6] gave (**4a**—**d**), in 80—83% yield, respectively. Reduction of (**4a**—**d**), followed by phenylsulphenylation by modification of Walker's method[7] afforded (**5a**—**d**) in 70—75% yield, respectively.

A benzene solution of (**5a**) (0.01 M) was heated under reflux in the presence of tri-n-butyltin hydride (1.5 equiv.) and a trace amount of azobisisobutyronitrile (AIBN) in the usual way[1,2] to give (**6a**) in 57% yield as a single diastereoisomer, m.p. 124—128 °C, *m/z* 231 (M^+). The determination of the stereochemistry of (**6a**) was based on the Dreiding model study and Karplus relation[8] of signals due to NCH_2 and PhC*H* in its ^1H n.m.r. spectrum ($CDCl_3$, 400 MHz). Of NCH_2, the lower NC*H* signal appeared at δ 3.79 (d, *J* 13.36 Hz) and the higher one at δ 3.24 (dd, *J* 2.88, 13.36 Hz). PhC*H* resonated at δ 3.03 (broad d, *J* 12.88 Hz) owing to the large diaxial and small axial–equatorial interaction. These facts indicate that Me is axially and Ph is equatorially oriented. The Me signals, which appeared at considerably high field, δ 0.76 (d, *J* 7.00 Hz) also support this assignment. Diastereoselectivity in this cyclisation can be accounted for by the effect of A-type strain[9] on the benzyl radical intermediates. Of the two possible intermediates (**7a**, **b**; R = Me), (**7b**) should be

† All new compounds gave satisfactory microanalyses and/or spectral data.



For (3)—(5)

(a); X = H, R = Me
(b); X = H, R = $CH_2CH{=}CH_2$
(c); X = H, R = $CH_2CH_2CH{=}CH_2$
(d); X = OMe, R = $CH_2CH_2CH{=}CH_2$

Scheme 1. *Reagents:* i, Lithium di-isopropylamide (LDA), tetrahydrofuran (THF), MeI[allyl bromide for (**2b**) and 1-iodobut-3-ene for (**2c**)], −78 °C—room temperature, 2 h; ii, $LiAlH_4$, Et_2O, 0 °C, 1 h; iii, $NaBH_4$, MeOH, 0 °C; iv, PhSSPh, Bu^n_3P, benzene, room temperature.

preferable to (**7a**) because of the steric repulsion of Me and Ph groups in (**7a**) in which Me is an equatorial substituent. The successive C–H bond formation *via* delivery of H to the less hindered face of the radical gave (**6a**). The same reaction using (**5b**) gave (**6b**) as a single diastereoisomer, yield 73%, m.p. 101—104 °C, *m/z* 257 (M^+). However, in the case of (**5c**), further cyclisation of the intermediate (**7c**) occurred to form (**8a**) in 57% yield, m.p. 128—131 °C, *m/z* (M^+), ^{1}H n.m.r. ($CDCl_3$, 400 MHz) δ 4.41 (1H, dd, *J* 8.48, 8.48 Hz), 3.97 (1H, dd, *J* 5.60, 8.48 Hz), 3.79 (1H, dd, *J* 1.48, 13.12 Hz), 3.01 (1H, dd, *J* 3.84, 13.12 Hz), 0.77 (3H, d, *J* 6.64 Hz). The ring-juncture of the 4a-phenylcyclopenta[*c*]pyridine ring was confirmed by the magnitude of the *J* value and the Karplus relation for the CH_2 signals at δ 3.79 and 3.01. Although the relative configuration of 5-Me was not determined at this stage, we assumed it to be *cis* to the Ph group from the intermediates (**7c**, **d**) for the second cyclisation. Of (**7c**, **d**), (**7c**) is more favourable than (**7d**) giving the *trans*-isomer. The considerably high field Me signal may support this assumption. In a similar way, (**8b**) was obtained from (**5d**) in 65% yield, m.p. 160—163 °C, *m/z* 301 (M^+), ^{1}H n.m.r. ($CDCl_3$, 400 MHz) δ 4.40 (1H, dd, *J* 8.40, 8.40 Hz), 3.96 (1H, dd, *J* 5.72, 8.40 Hz), 3.81 (3H, s), 3.67 (1H, dd, *J* 1.32, 13.60 Hz), 3.01 (1H, dd, *J* 3.84, 13.60 Hz), 0.76 (3H, d, *J* 6.72 Hz).

The method described in this paper should be widely applicable to the synthesis of condensed aza-polycyclic compounds.

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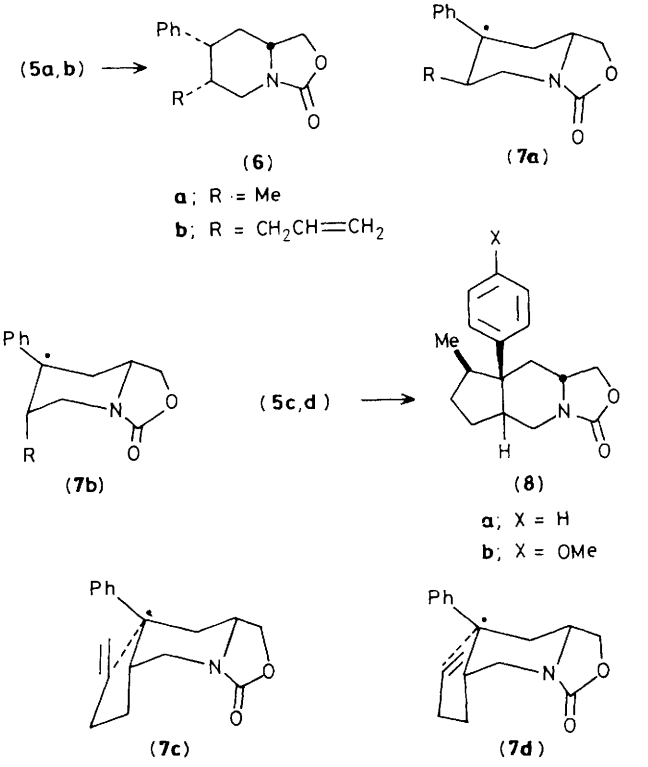

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