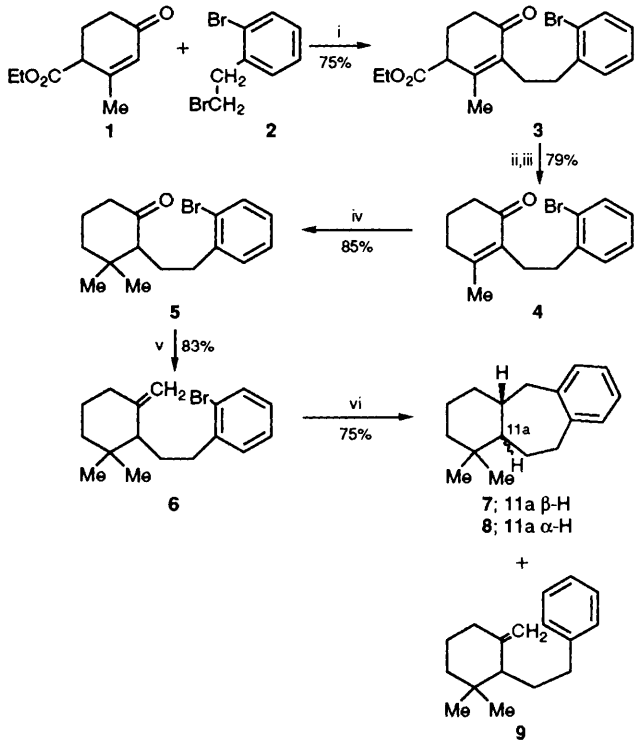
Highly Regioselective 7-*endo*-Aryl Radical Cyclisation: Synthesis of Octahydro-2*H*-dibenzo[*a,d*]cycloheptenes

Ajit K. Ghosh, Keya Ghosh, Sitaram Pal and Usha Ranjan Chatak*

Department of Organic Chemistry, Indian Association for the Cultivation of Science, Jadavpur, Calcutta–700 032, India

A highly efficient 7-*endo-trig*-aryl radical cyclisation of the alkene **6** and the vinylcyclohexanols **11a–d** with tri-n-butyltin hydride leading to the respective octahydro-2*H*-dibenzo[*a,d*]cycloheptene derivatives **7** and **8** and **12a–d** is reported.

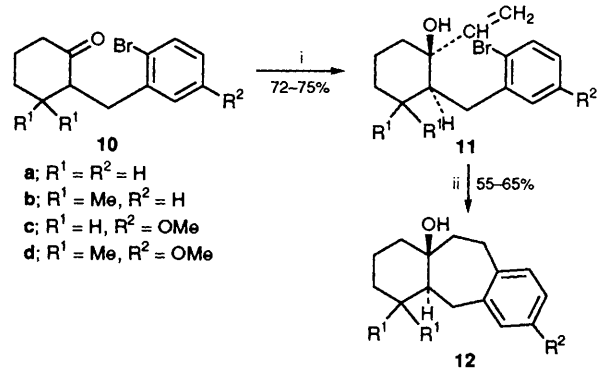
Intramolecular free radical cylisation reactions have emerged as extremely useful synthetic methods for five- and six-membered carbocyclic ring systems.[1] Although tri-n-butyltin hydride (TBTH)-induced free radical cyclisations have been successfully extended to the construction of macrocarbocycles,[2] until recently, no definitive report existed for the formation of seven-membered carbocycles[3,4] under such reaction conditions except for a few examples[5] where a heteroatom replaced a methylene group in the newly formed rings. A tandem TBTH-induced acyl radical cyclisation has been reported recently[6] for the synthesis of a cycloheptanone ring system. Cycloheptene derivatives have been synthesised recently by tandem oxidative free radical cyclisations using manganese(III)[7] and cobalt(I)[8] reagents. We have demonstrated[9] an exclusive 6-*endo-trig*-aryl radical cyclisation in the TBTH-induced reactions of some 2-(*o*-bromobenzyl)methylenecyclohexanes to the respective *trans*-octahydroanthracenes, through preferred radical attack at the least substituted exocyclic methylene carbon centre. We now report preliminary results revealing that such a strategy may



Scheme 1 *Reagents*: i, $Bu^tO^-K^+$, Bu^tOH; ii, KOH–H_2O–EtOH; iii, HCl 6 mol dm^{-3}; iv, $LiMe_2Cu$–BF_3·Et_2O; v, $Ph_3P^+MeI^-$, *tert*-$C_5H_{11}O^-Na^+$ in toluene; vi, Bu^n_3SnH, AIBN, C_6H_6

be efficiently employed in cycloheptene ring annulations involving 7-*endo*-*trig*-aryl radical cyclisation leading to a simple route to partially reduced dibenzo[*a*,*d*]cycloheptenes.

The sequence is first illustrated by the transformation of the alkene **6** to a mixture of the *cis*- and *trans*-octahydro-2*H*-dibenzo[*a*,*d*]cycloheptens **7** and **8** (Scheme 1). The easily accessible *gem*-dimethylcyclohexanone **5** was smoothly transformed to the desired alkene **6**† by Wittig reaction under forcing conditions.[10] The cyclohexanone **5** was prepared in a good yield from the cyclohexenone **4**, which was obtained by alkylation of Hagemann's ester **1** with the bromide **2** and then hydrolytic decarboxylation of the alkylated product **3** following a standard procedure.[11] The radical cyclisation of the alkene **6** in refluxing benzene (0.013 mol dm^{-3} solution) for 10 h with TBTH (1.1 equiv.) and a catalytic amount of azoisobutyronitrile (AIBN) furnished a 9:1 mixture (GLC and ^1H NMR spectroscopy) of the *cis*- and *trans*-hydrocarbons **7** and **8** and the known debrominated olefin **9**[10] in 75% yield, after separation of the tin compounds[12] by treatment with saturated aqueous KF followed by silica gel chromatography. Purification of the mixture on silica gel after hydroboration and then oxidation with alkaline hydrogen peroxide[10] completely eliminated the olefin **9** and afforded an inseparable mixture of the epimeric hydrocarbons **7** and **8** in a ratio of *ca.* 45:55 (^1H NMR spectroscopy). The structural and stereochemical assignments for **7** and **8** in this mixture followed directly from ^1H NMR spectroscopic comparison with the pure *cis*-isomer **7**.‡



Scheme 2 *Reagents*: i, CH_2=CHMgBr, tetrahydrofuran; ii, Bu^n_3SnH, AIBN, C_6H_6

The stereochemical outcome in the 7-*endo*-*trig* cyclisation of **6** leading to a mixture of the *cis*- and *trans*-hydrocarbons **7** and **8** unlike that observed[9] in the 6-*endo*-*trig* cyclisation in the lower homologous leading only to the respective *trans*-products, is possibly due to the increase flexibility in the former case in lowering the transition states energy in the formation of respective *cis*- and *trans*-products.

The scope of the 7-*endo*-*trig*-aryl radical cyclisation was further extended to the vinylcyclohexanols **11a–d** (Scheme 2). The cyclohexanols **11a**, **11b**, **11c** and **11d** were obtained as a single epimer in each case, in excellent yields, by condensation with the easily accessible cyclohexanones **10a**,[9] **10b**,[9] **10c**§ and **10d**§ with vinylmagnesium bromide in tetrahydrofuran after purification by chromatography on basic alumina. The stereochemical homogeneity of each of these alcohols followed from GLC analyses and ^1H NMR spectroscopy and the assigned stereostructure is based upon analogy.[13]

The radical cyclisation of the vinylcyclohexanols **11a–d** in refluxing benzene (0.01 mol dm^{-3} solution) for 6–8 h with TBTH (1.3 equiv.) and a catalytic amount of AIBN afforded the respective pure tricyclic alcohols **12a–d** in 55–65% yields, after removal of the tin compounds followed by chromatography on silica gel. The assigned structure for each of the products resulting from 7-*endo*-*trig* cyclisation was based upon spectroscopic data.

The intrinsic preference for an 7-*endo*-*trig*-aryl radical cyclisation in the least substituted terminal carbon atom of a double bond, established in the present work, is noteworthy both synthetically and mechanistically. Further studies on this novel radical cyclisation towards some natural products[14] incorporating the dibenzo[*a*,*d*]cycloheptene ring systems are under way.

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† Compounds described here are all racemates. Satisfactory elemental analyses were obtained for new compounds. Selected spectroscopic data: **6** ^1H NMR δ (CCl_4, 60 MHz) 0.85 (s, 3H, Me), 0.94 (s, 3H, Me), 1.2–2.84 (m, 11H), 4.68–4.88 (m, 2H, C=CH_2) and 7.0–7.56 (m, 4H, ArH). **7** and **8** ^1H NMR δ (CCl_4, 60 MHz) 0.72 and 0.92 (each s, Me for *cis*-isomer), 0.86 and 1.03 (each s, Me for *trans*-isomer), 1.16–2.90 (m, CH_2 and CH), and 6.97 (br s, ArH); MS (EI) *m*/*z* 228 (M^+, 100%), 214 (36), 179 (77), 129 (82) and 104 (84). **12a** ^1H NMR δ ($CDCl_3$, 200 MHz) 0.90–2.20 (m, 11H), 2.40–2.65 (m, 3H), 3.25–3.40 (m, 2H) and 7.15 (s, 4H, ArH); MS (EI) *m*/*z* 216 (M^+, 34%), 198 ($M^+ - H_2O$, 100), 129 (68), 117 (58) and 91 (66). **12b** ^1H NMR δ ($CDCl_3$ 200 MHz) 1.04 (s, 3H, Me), 1.06 (s, 3H, Me), 1.08–2.00 (m, 9H), 2.28–3.40 (m, 5H) and 7.12 (br s, 4H, ArH); MS (EI) *m*/*z* 244 (M^+, 30%), 226 ($M^+ - H_2O$, 100), 156 (47), 118 (83) and 91 (45). **12c** ^1H NMR δ ($CDCl_3$) 0.80–2.20 (m, 11H), 2.30–2.60 (m, 3H), 3.20–3.30 (m, 2H), 3.80 (s, 3H, ArOMe), 6.60–6.80 (m, 2H, ArH) and 7.05 (d, *J* 9 Hz, 1H, ArH); MS (EI) *m*/*z* 246 (M^+, 53%), 228 ($M^+ - H_2O$, 61), 213 (37), 159 (37) and 148 (100). **12d** ^1H NMR δ ($CDCl_3$, 200 MHz) 1.04 (s, 3H, Me), 1.06 (s, 3H, Me), 1.08–2.49 (m, 14H), 3.78 (s, 3H, ArOMe), 6.68–6.79 (m, 2H, ArH) and 7.0 (d, *J* 9 Hz, 1H, ArH).

‡ The pure *cis*-isomer **7** [^1H NMR δ (CCl_4, 60 MHz) 0.72 (s, 3H, CH_3), 0.92 (s, 3H, CH_3), 1.10–1.90 (m, 10H), 2.10–2.90 (m, 4H) and 6.97 (br s, 4H, ArH)] was prepared by Pd–C (10%) catalysed hydrogenolysis of the alcohol in ethanol, derived from $NaBH_4$ in ethanol reduction of (±)-*cis*-1,1-dimethyl-1,2,3,4,4a,10,11,11a-octahydrodibenzo[*a*,*d*]cyclohepten-5-one (ref. 10).

§ These ketones were prepared by procedures identical to those described for the corresponding demethoxy analogous (ref. 9).

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