SHORT PAPER

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Indium-mediated barbier allylations of hydroxyanthraquinones: an expedient synthesis of novel 10-alkenyl-10-hydroxy-9(10*H*)-anthracenones

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Indium-mediated allylations of 1,8-dihydroxy-9,10-anthraquinone with allyl, cinnamyl and crotonyl bromides/chlorides and 1,4- and 1,5- dihydroxy derivatives with allyl bromide in THF–MeOH–H_2O gave the respective 10-alkenyl-10-hydroxy-9(10H)-anthracenones in excellent yields.

Anthracenones substituted at C-10 have attained paramount significance[1] due to their broad spectrum biological activities including antipsoriatic activity and leukotriene biosynthesis inhibition. Naturally occuring[2] 1,8-dihydroxy-9(10*H*)-anthracenones, (R)- and (S)- aloin A and B derivatives (Fig. 1) possess a hydroxy group at C-10. Chemical transformation of hydroxyanthraquinones leads to the formation of either 9,10-dihydroxyanthracenes or 9- / 10-deoxyanthracenones[3] and the formation of 10-hydroxyanthracenones is not known. In the case of hydroxyanthraquinones, the poor reactivity of C=O and the ease in generation of oxa anions under basic conditions have restricted the addition of carbon nucleophiles. In the last few years, indium-mediated Barbier-type reactions have shown immense potential for allylations even on hydroxy carbonyl substrates.[4] We have found that indium-mediated allylations of dihydroxy-9,10- anthraquinones with their phenolic OH groups provide a unique methodology for the synthesis of 10-alkenyl-10-hydroxy-9(10H)-anthracenone derivatives.

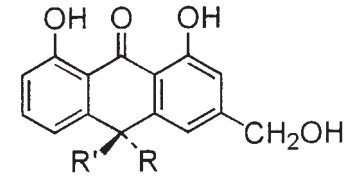

Fig. 1

The reaction of 1,8-dihydroxy-9,10-anthraquinone (**1**) with allyl bromide (**5**) and indium metal in THF – MeOH -H_2O (5 : 5 : 1) at 30–32ºC provided two isomeric compounds, M^+ *m/z* 282, 8 (90%), m.p. 121–23ºC and **14** (5%), thick liquid, after hydrolysis with aqueous hydrochloric acid. In their ^{1}H NMR spectra, both the compounds exhibit two doublets and one triplet due to the anthracenone ring. In the case of the major, higher R_f, component, the triplet due to C-3 and C-6H being *para* to a carbonyl group appears as the most downfield signal (δ 7.51) and its phenolic OH appears at δ 12.04 due to H-bonding with carbonyl. In the ^{1}H NMR of the minor component the doublet due to ArH *ortho* to carbonyl appears as the most downfield signal (δ 7.78) and the phenolic OH signal is shifted upfield to δ 8.17 due to lack of H-bonding. These spectral data conform to structures **8** and **14**, respectively for major and minor components. The formation of **8** as the major component could be attributed to the lesser steric hindrance at C_{10}=O than at C_9=O in **1**. This reaction failed to proceed in THF – H_2O (Barbier) and in dry THF (both Barbier and Grignard) conditions.

The reaction of **1** with cinnamyl bromide failed to proceed at 30ºC but on increasing the reaction temperature to 40-45ºC gave anthracenone 9 (82%). In its ^{1}H NMR spectrum, the appearance of a 2H doublet at δ 2.65 confirms it as the alpha addition product and the corresponding *gamma* addition product could not be detected. 3-Chlorobutene with **1** gave a compound (30%), m.p. 83ºC, M^+ m/z 296 which in its ^{1}H NMR spectrum exhibits two Me doublets at δ 0.78 and 1.50 in 9:1 ratio along with other signals and could be a mixture of **10** and **15** which could not be separated. Therefore, in indium-induced reactions of substituted allyl bromides, *alpha* addition is the prefered route over *gamma* addition. 9,10-Anthracenone (**4**) and its 1,4- (**2**) and 1,5- (**3**) dihydroxy derivatives gave the respective anthracenones **13**, **11** and **12** in good yields with allyl bromide.

Cinnamyl bromide and **2** did not give the desired addition product but formed leucoquinazirine (60%) – the reduced product of **2**, cinnamyl alcohol and cinnamyl methyl ether. The preformed cinnamyl indium complex also reacts with **2** in dry THF to give leucoquinazirine (70%) and cinnamyl alcohol. Probably, the cinnamyl indium complex transfers an electron to reduce **2** and itself is converted to a radical cation which is quenched with the solvent to give cinnamyl alcohol / cinnamyl methyl ether.

Therefore, indium-mediated Barbier allylations of α,ω-dihydroxy-9,10-anthraquinones provide the respective 10-alkenyl-10-hydroxy-9(10H)anthracenones in excellent yields and, presumably due to the poor basicity of the indium reagents, even the acidic phenolic OH groups do not interfere.

A preliminary screening profile shows that cancer cell lines NCI-H460, MCF-7 and SF-268 show less than 35 % growth with **8**, **11** and **12** and show –53 to –73% growth with **9** at 10^{-4}M concentration.

Experimental

For general experimental see ref 5.

Barbier allylations of 9,10-anthraquinones (**1–4**): general procedure: In a typical experiment 1,8-dihydroxyanthraquinone (750 mg, 3.1 mmol), allyl bromide (654 mg, 5.4 mmol) and indium metal (413 mg, 3.6 mmol) were taken in a THF (10ml) – CH_3OH (10ml) – water (5 ml) mixture and the reaction mixture was stirred at 30±2^{0}C for about 4–6 h. The reaction mixture was then quenched with saturated brine solution and dilute HCl until it became clear. It was extracted ($CHCl_3$), the extract was dried (Na_2SO_4) and the solvent was removed. The residue was column chromatographed (silica gel, 60–120 mesh) to isolate pure **8** and **14**. A similar procedure was followed for all the reactions except when stated.

10-[1-(prop-2-enyl)]-1,8,10-trihydoxy-9(10H)-anthracenone (**8**): (90%), yellow solid, m.p. 121–23ºC (ethyl acetate : methanol); M^+ *m/z* 282 (M^+); ^{1}H NMR ($CDCl_3$): δ 2.56(1H, s, OH), 2.59–2.62 (2H,

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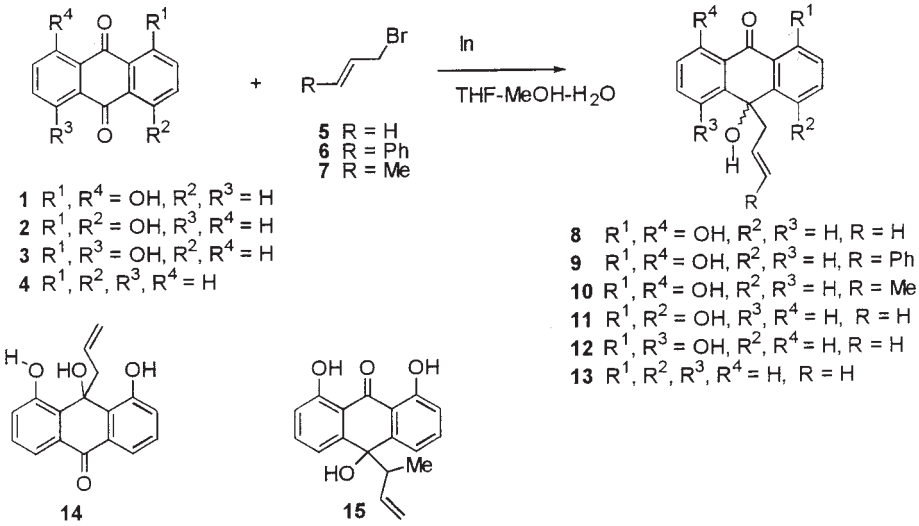
† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*



m, CH_2), 4.58–4.90 (2H, m, =CH_2), 5.10–5.24 (1H, m, =CH), 6.83 (2H, d, J = 8.2, H-2,7), 7.32 (2H, d, *J* = 8.2, H-4,5), 7.51 (2H, t, *J* = 8.2, H-3,6), 12.04 (2H, s, 2 × OH); ^{13}C NMR (normal/DEPT - 135) ($CDCl_3$) : δ 54.23 (-ve, CH_2), 72.96 (ab, C), 114.32 (ab, C), 116.8 (+ve, CH), 119.87 (-ve, CH_2), 130.84 (+ve, CH), 136.58 (+ve, CH), 148.58 (ab, C), 161.77 (ab, C), 192.13 (ab, C). λ_{max} (EtOH): 374 (8×10^2), 299 (7.4×10^2), 267 (6.2×10^2)nm. (Found C 72.6; H 4.7%. $C_{17}H_{14}O_4$ requires C 72.34; H 4.96%).

10-[1-(3-phenylporp-2-enyl)]-1,8,10-trihydoxy-9(10H)-anthracenone (**9**): The reaction was performed at 40 ± 2°C. (82%); yellow solid; m.p. 179°C (ethyl acetate – methanol); M^+ *m/z* 358(M^+); ^{1}H NMR ($CDCl_3$): δ 2.51 (1H, s, OH), 2.65 (2H, d, *J* = 7.5, CH_2), 5.51–5.67 (1H, m, =CH), 5.92 (1H, m,CH), 6.87 (2H, d, *J* = 8.4, H-2,8), 7.04–7.24 (5H, m, Ph), 7.34 (2H, d, *J* = 8.4, H-4,5), 7.52 (2H, t, *J* = 8.4, H-3,6), 12.00 (2H, s, 2 × OH); ^{13}C NMR (normal / DEPT-135) ($CDCl_3$) : δ 53.41 -ve, CH_2), 73.62 (ab, C), 114.17 (ab, C), 116.57 (+ve, CH), 117.07 (+ve. CH), 122.39 (+ve, CH), 126.01 (+ve, CH), 127.42 (+ve, CH), 128.39 (+ve, CH), 135.02 (+ve, CH), 136.47 (+ve, CH), 136.67 (ab, C), 148.69 (ab, C), 162.18 (ab, C), 192.02 (ab, C). λ_{max} (EtOH): 374 (8.7×10^2), 294 (9.4×10^2), 253 (2.2×10^3) nm. (Found C 76.8; H 4.8%. $C_{23}H_{18}O_4$ requires C 77.09; H 5.03%)

10-[3-(but-1-enyl)]-1,8,10-trihydoxy-9(10H)-anthracenone (**10**/**15**): The reaction was performed at 50 ± 2°C and took 12h for completion. (30%), m.p. 83°C (CH_2Cl_2 – MeOH); M^+ *m/z* 296(M^+); ^{1}H NMR ($CDCl_3$): δ 0.78(1/10 3H, d, *J* = 6.8Hz, CH_3), 1.50 (9/10 3H, d, *J* = 6.2Hz, CH_3), 2.42–2.65(2H, m, CH_2), 4.73–5.09 (2H, m, CH_2), 5.30–5.48 (1H, m, =CH), 6.88–6.95 (2H, m, anth -H), 7.21–7.41 (2H, m, anth - H), 7.51–7.58 (2H, m, anth - H), 12.01, 12.04 (2H, s, OH). (Found C 73.1; H 5.3 %. $C_{18}H_{16}O_4$ requires C 72.97; H 5.41%).

10-[1-(prop-2-enyl)]-1,4,10-trihydoxy-9(10H)-anthracenone (**11**): (97%) brown solid, m.p. 108°C (CH_2Cl_2 – MeOH); M^+ *m/z* 282 (M^+); ^{1}H NMR ($CDCl_3$): δ 2.63–3.07 (2H, m, CH_2), 3.39 (s, 1H, OH), 4.52–4.80 (2H, m, =CH_2), 4.94–5.12(1H, m, =CH), 6.74 (1H, d, *J* = 9.0, H-3), 7.00 (1H, d, J = 9.0, H-2), 7.47 (1H, t, *J* = 7.6, H-6), 7.67 (1H, t, *J* = 7.6, H-7), 7.78 (1H, d, *J* = 7.6, H-5), 8.14 (1H, d, J = 7.6, H-8), 8.30(s, 1H, OH), 12.39 (s, 1H, OH); ^{13}C NMR (normal/DEPT -135) ($CDCl_3$) : δ 48.27 (-ve, CH_2), 74.47 (ab, C), 114.16 (ab, C), 118.01 (+ve, CH), 120.03 (-ve, CH_2), 125.23 (+ve, CH), 126.41 (+ve, CH), 126.53 (+ve, CH), 127.01 (ab, C), 128.24 (+ve, CH), 129.75 (ab, C), 130.57 (+ve, CH), 134.13 (+ve, CH), 145.39 (ab, C), 147.36 (ab, C), 156.08 (ab, C), 187.86 (ab, C). λ_{max} (EtOH): 513 (7.3×10^2), 466 (4.16×10^3), 274 (11.1×10^3), 256 (10.6×10^3) nm. (Found C 72.7; H 5.2 %. $C_{17}H_{14}O_4$ requires C 72.34; H 4.96%)

10-[1-(prop-2-enyl)]-1,5,10-trihydoxy-9(10H)-anthracenone (**12**): (96%), yellow solid, m.p. 172°C (ethyl acetate - MeOH); M^+ *m/z* 282 (M^+); ^{1}H NMR ($CDCl_3$): δ 2.70–3.07 (2H, m, CH_2), 3.36 (1H, s, OH), 4.60–4.89 (2H, m, =CH_2), 4.96–5.13 (1H, m, =CH), 6.90 (1H, d, *J* = 8.2Hz, anth-H), 7.21 (1H, d, *J* = 8.2, anth -H), 7.28 (1H, d, *J* = 8.2, anth-H), 7.42 (1H, t, *J* = 8.2Hz, anth -H), 7.54 (1H, t, *J* = 8.2Hz, anth-H), 7.82 (1H, d, *J* = 8.2Hz, anth-H), 8.86 (1H, s, OH), 12.79 (s, 1H, OH); ^{13}C NMR (normal / DEPT - 135) ($CDCl_3$): δ 49.47(-ve, CH_2), 74.52 (ab, C), 116.02 (+ve, CH), 116.5 (+ve, CH), 118.28(+ve, CH), 119.76 (-ve, CH_2), 122.24 (+ve, CH), 128.92 (+ve, CH), 130.99 (+ve, CH), 135.97 (+ve, CH), 155.40 (ab, C), 162.35 (ab, C), 187.86 (ab, C). λ_{max} (EtOH): 343 (7×10^2), 293 (11.1×10^2), 269 (9×10^2) nm. (Found C 72.0; H 5.0 %. $C_{17}H_{14}O_4$ requires C 72.34; H 4.96%)

10-[1-(prop-2-enyl)]-10-hydroxy-9(10H)-anthracenone (**13**): (83%); yellow solid, m.p. 106°C (CH_2Cl_2 -MeOH) (Lit.[6] m.p. 108°C); M^+ *m/z* 250 (M^+); ^{1}H NMR ($CDCl_3$): δ 2.63(1H, s, OH); 2.68(2H, d, *J* = 7.4Hz, CH_2), 4.53–4.84(2H, m, =CH_2), 5.02–5.20 (1H, m, =CH), 7.41 (2H, t, *J* = 8.4Hz, H-3,6), 7.64 (2H, t, *J* = 8.4Hz, H-2,7), 7.88 (2H, d, *J* = 8.4Hz, H-4,5), 8.15 (2H, d, *J* = 8.4Hz, H-1,8); ^{13}C NMR (normal/DEPT - 135) ($CDCl_3$): δ 52.86 (-ve, CH_2), 72.21(ab, C), 119.46 (-ve, CH_2), 125.66 (+ve, CH), 126.33 (+ve, CH), 127.41 (+ve, CH), 130.35 (+ve, CH), 130.91(ab, C), 133.04 (+ve, CH), 146.85 (ab, C), 183.24 (ab, C). λ_{max}(EtOH): 274 (1.64×10^3) nm.

10-[1-(prop-2-enyl)]-1,8,9-trihydoxy-10(9H)-anthracenone (**14**): (5%), thick oil, M^+ *m/z* 282 (M^+); ^{1}H NMR ($CDCl_3$): δ 3.14 (2H, d, *J* = 7.2, CH_2), 4.50–4.74 (2H, m, =CH_2), 4.85–5.05 (1H, m, =CH), 5.61 (1H, s, OH), 7.16 (2H, d, *J* = 8.0, H-2,7), 7.36 (2H, t, *J* = 8.0, H-3,6), 7.78 (2H, d, *J* = 8.0, H-4,5), 8.17 (2H, s, 2 × OH); ^{13}C NMR (normal/DEPT - 135) ($CDCl_3$): δ 44.67 (-ve, CH_2), 76.37 (ab, C), 119.25 (+ve, CH), 120.30 (-ve, CH_2), 124.66 (+ve, CH), 128.84 (ab, C), 129.40 (+ve, CH), 130.84 (+ve, CH), 131.54 (ab, C), 154.51 (ab, C), 184.26 (ab, C).

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Paper 99/163

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