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Synthesis of Tamoxifen and 4-Hydroxytamoxifen using Super-base-metalated Propylbenzene

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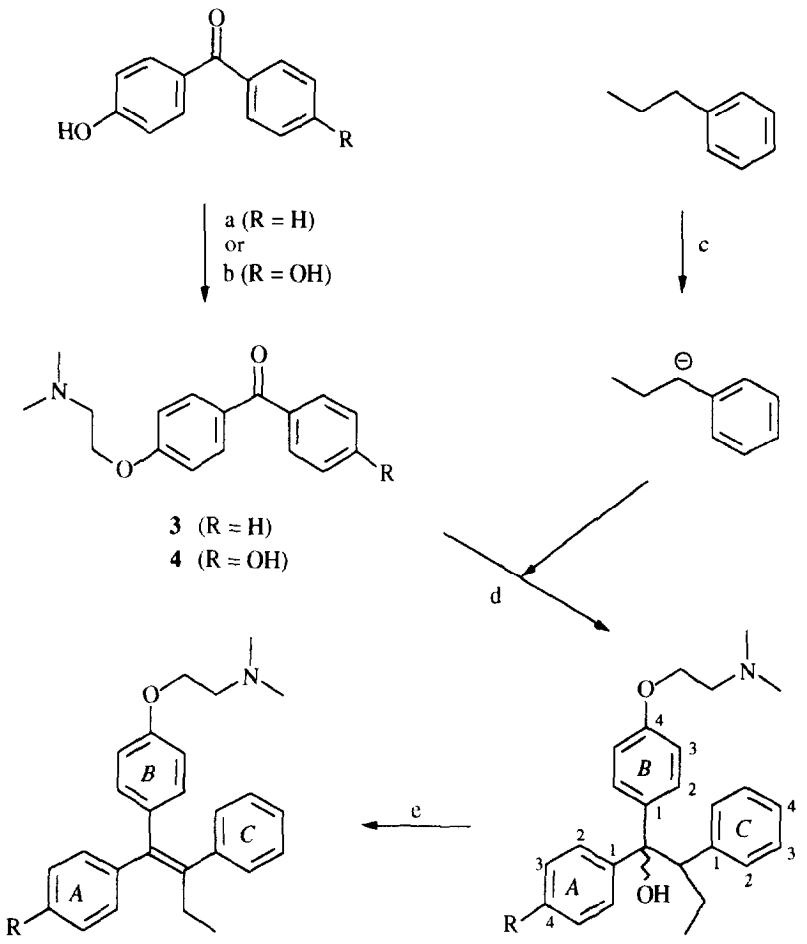
Abstract: Propylbenzene is metalated regioselectively at the α-carbon using the *n*-BuLi–*t*-BuOK–TMEDA super-base combination; the resulting carbanion condenses with functionalised benzophenones to provide direct syntheses of tamoxifen and 4-hydroxytamoxifen.

The non-steroidal antiestrogen Tamoxifen **1** (Nolvadex®) (TAM) has for two decades been the most important chemotherapeutic agent for the treatment of breast cancer.[1] Its primary metabolite **2** (HTAM), which is 4-hydroxylated in the *A*-ring, has a greater affinity for the estrogen receptor than TAM, and may contribute to the *in vivo* antitumour activity. Among the different synthetic approaches which have been used for the preparation of TAM derivatives,[2] only one example of a disconnection across the olefinic bond to give an *A,B*-ring electrophile and a *C*-ring nucleophile has been described,[2a] involving the inefficient (7% yield) condensation of a (1-phenyl)propyl Grignard reagent with a simplified benzophenone.

Super-basic reagents,[3] usually binary combinations such as alkylsodium–TMEDA or alkyllithium–*t*-BuOK, are known to metalate alkyl-substituted benzenes at the α-carbon centres and/or the aromatic ring. The resulting highly reactive nucleophilic carbanions have been used in only a small number of synthetic applications,[4] generally involving reactions with very simple electrophiles (*e.g.* alkyl halides, CO_2). Regioselective metalation of a benzylic centre is an important challenge in synthetic organic chemistry,[5] and the *n*-BuLi–*t*-BuOK (LICKOR) reagent developed by Schlosser[3b] has been shown to give good selectivity in the deprotonation of an ethylarene at the α-carbon.[4a]

We present herein a direct synthesis of both TAM and HTAM (Scheme) in which the key step is the condensation of a fully functionalised benzophenone with the previously undescribed anion of propylbenzene, generated from the arene by a three-component super-basic medium. The ketones **3** and **4** bearing the basic side chain were each prepared in 65% yield by alkylation of the commercially available 4-hydroxy- and 4,4'-dihydroxy- benzophenones with 2-chloroethyldimethylamine.



a: $ClCH_2CH_2NMe_2 \cdot HCl$, 2 equiv K_2CO_3, DMF, 5 h, 110°C
b: $ClCH_2CH_2NMe_2$, 2 equiv NaH, DMF, 2 h, 110°C
c: *n*-BuLi, *t*-BuOK, TMEDA, hexane, rt, argon atmosphere
d: **3** or **4**, Et_2O, added to 6 equiv of anion at –70 °C; then 0 °C, 5 h
e: 32% H_2SO_4, 16 h, 50 °C

SCHEME

The only previous use of the triple super-base combination *n*-BuLi–*t*-BuOK–TMEDA was the successful metalation of ethylene.[6,7] We have found that this super-base combination also allows facile generation of a stable, deep red carbanion from propylbenzene in hexane at room temperature under argon. Subsequent addition of an ethereal solution of ketone **3** or **4** to an excess (6 equivs) of this anion at –70 °C gave the corresponding carbinols **5** or **6** as mixtures of stereoisomers. No trace of triphenylmethanol-type structural isomers was found, indicating that propylbenzene had been regioselectively metalated at the α-carbon centre. This observation concurs with the excellent regioselectivity of the LICKOR reagent.[4a] Mineral acid was used to effect dehydration of **5** and **6** to give the title products **1** and **2** respectively, each as a *cis:trans* mixture (1:1),[8] in good overall yield for the two steps: 50% for TAM and 70% for HTAM.[9]

The reactivity of super-base-metalated propylbenzene compared favorably with the corresponding Grignard and Wittig reagents: treatment of ketone **3** with 1-(phenyl)propyl magnesium bromide failed to give any condensation products, while $(Ph_3PCHPhCH_2CH_3)Br$/NaH reacted with **3** to give *cis/trans*-**1** in only 5% yield. The short procedure described here represents a useful synthetic application of a super-base-generated carbanion, and shows its reactivity to be highly chemoselective with polyfunctional electrophilic substrates. Further exploration of the synthetic scope of such reactive species is underway.

Procedure for condensation reactions involving the propylbenzene anion. To a stirred suspension of 95 % potassium *t*-butoxide (1.98 g, 16.8 mmol) in hexane (10 ml) under argon at rt was added propylbenzene (2.35 ml, 16.9 mmol), *n*-butyllithium solution (1.6 M in hexane; 10.5 ml, 16.8, mmol), then TMEDA (5.1 ml, 33.8 mmol). The resulting bright red suspension was stirred for a further 30 min at rt, then cooled to –70 °C. A solution of the selected ketone (2.8 mmol) in ether or THF (10 ml) was added *slowly* (over 20-30 min) then the mixture was allowed to warm to rt over 3 h. Standard quenching (aqueous ammonium chloride solution) and extraction procedures (dichloromethane) followed by flash chromatography on silica gel gave the product carbinols as inseparable mixtures of diastereoisomers.[10]

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7. It appears that this super-base combination may also be used to metalate norbornene and norbornadiene; see the footnote in: Verkruijsse, H. D.; Brandsma, L. *Recl. Trav. Chim. Pays-Bas*, **1986**, *105*, 66-68.
8. The facile *cis-trans* isomerisation of TAM and HTAM renders potentially stereoselective syntheses unattractive; almost all preparations of TAM derivatives, including the commercial process, involve a final separation of *Z* and *E* isomers by fractional crystallisation of salts.
9. Physicochemical data were consistent with proposed structures and/or identical to authentic materials.
10. Spectral data for new carbinols (as diastereoisomeric mixtures): **5** — ^{1}H NMR ($CDCl_3$; 300 MHz) δ (ppm): 0.72 and 0.75 (3 H, 2t, each J = 7.4 Hz, CH_3); 1.78 (2 H, m, CH_2); 2.29 and 2.34 (6 H, 2s, $N(CH_3)_2$); 2.74, (2 H, m, NCH_2); 3.64 and 3.68 (1 H, 2t, each J = 7.4 Hz, CH); 4.06 (2 H, m, OCH_2); 6.63 (2 H, d, J = 8.8 Hz, H-3*B*); 6.89 (2 H, d, J = 8.8 Hz, H-2*B*); 7.01-7.55 (10 H, m, H-arom.); ^{13}C NMR ($CDCl_3$; 75 MHz) δ (ppm): 12.6 (CH_3); 23.3 (CH_2); 45.8 (NCH_3); 56.3 (CH); 58.1 (NCH_2); 65.6 and 65.7 (OCH2); 80.5 (COH); 113.4 and 113.5 (C-3*B*); 125.6, 125.8, 126.2, 126.4, 126.9, 127.5, 127.8, 127.9, 129.1 and 130.0 (C-2*ABC*, C-3*AC*, C-4*AC*), 138.8 and 139.8 (C-1*AC*), 146.1 (C-1*B*), 157.4 (C-4*B*); MS (CI/NH_3) m/z: 390 $[MH]^+$. **6** — ^{1}H NMR ($CDCl_3$; 300 MHz) δ (ppm): 0.72 (3 H, m, CH_3); 1.67 (2 H, m, CH_2); 2.13 and 2.19 (6 H, 2s, $N(CH_3)_2$); 2.51 and 2.61 (2 H, 2t, J = 5.4 Hz, NCH_2); 3.31 and 3.33 (1 H, 2t, J = 5.1 Hz, CH); 3.78 and 3.94 (2 H, 2t, J = 5.4 Hz, OCH_2); 6.31 and 6.54 (2 H, 2d, each J = 8.7 Hz, H-3*B*); 6.43 (2 H, d, J = 8.9 Hz, H-3*A*); 6.66-6.96 (5 H, m, H-arom.); 7.27 (2 H, d, J = 8.7 Hz, H-2*B*); 7.34 (2 H, d, J = 8.9 Hz, H-2*A*); ^{13}C NMR ($CDCl_3$; 75 MHz) δ (ppm): 13.0 (CH_3); 24.9 (CH_2); 45.8 (NCH_3); 58.1 (CH); 59.0 and 59.1 (NCH_2); 66.3 and 66.5 (OCH2); 81.7 (COH); 114.0, 114.7, 114.8 and 115.5 (C-3*AB*); 126.7 (C-4*C*), 126.7, 128.1, 128.5, 129.0 and 131.7 (C-2*ABC*, C-3*C*); 139.1 (C-1*C*); 141.1, 141.4, 142.4 and 142.5 (C-1*AB*); 156.1, 156.8, 157.8 and 158.5 (C-4*AB*); MS (CI/NH_3) m/z: 406 $[MH]^+$.

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