SYNTHESIS OF *C*-RING AZA-ANALOGUES OF TAMOXIFEN

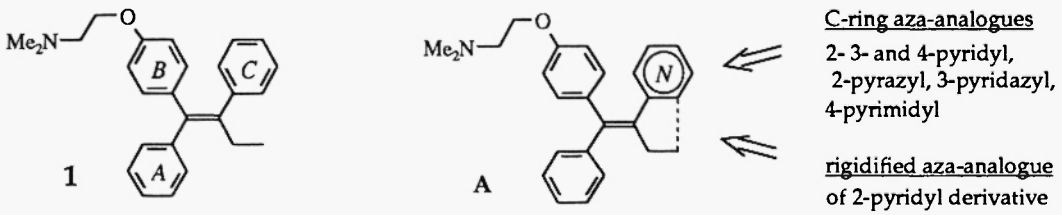
Chantal Olier-Reuchet, David J. Aitken* and Henri-Philippe Husson*

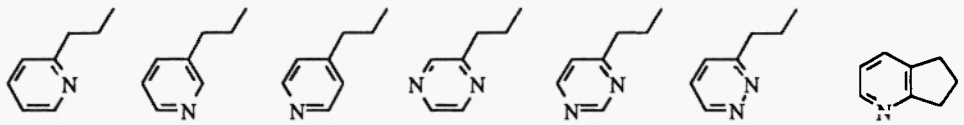
Laboratoire de Chimie Therapeutique associé au CNRS, Faculté des Sciences Pharmaceutiques et Biologiques, Universite Rene Descartes, 4 Avenue de l'Observatoire, 75270 Paris cedex 06, France.
Fax: +33-1 43-29-14-03 E-mail: aitken@pharmacie.univ-paris5.fr

Abstract: Short syntheses of seven C-ring nitrogen heterocycle analogues of Tamoxifen are presented. The key reactions involve condensation of a metallated propylazine with a functionalized benzophenone, followed by dehydration of the resulting carbinol, avoiding a retrocondensation process.

The anti-estrogen Tamoxifen **1** is the most important drug for the treatment of hormone-dependent breast cancer.[1] In the search for second generation analogues with higher and more selective activity, a wide variety of modifications to the parent triarylethylene structure have been investigated. Although the *B*-ring's basic side chain is necessary for anti-estrogen activity, and only tolerates minor alteration, some promising new derivatives have emerged from modifications at other sites in the structure. The knowledge that Tamoxifen is metabolized to the active *A*-ring 4-hydroxy and 3,4-dihydroxy derivatives has inspired the investigation of a large number of *A*-ring substituents, leading to development and clinical trials of a 3-hydroxy compound Droloxifen[2] and a 4-iodo derivative Idoxifen.[3] Modifications of the ethyl group has revealed some useful derivatives, including the drug Toremifen[4] which has a 2-chloroethyl chain. Relatively little work has been concentrated on the modification of the *C*-ring, although recently it was shown that a *C*-ring 4-amino substituent improves the estrogen receptor binding affinity of Idoxifen.[5] This suggests an interest in the preparation of Tamoxifen analogues of general structure **A** in which the *C*-ring is replaced by an isosteric heterocyclic aromatic ring having the possibility to form a hydrogen bond. This kind of heterocyclic replacement has so far only been studied for Tamoxifen's *A*-ring.[6]

In this communication, we present the synthesis of seven such analogues, following a synthetic strategy requiring a disconnection across the olefinic bond, which implies a benzophenone-type electrophile to supply the *A* and *B* rings. This uncommon approach for the synthesis of Tamoxifen derivatives appeared suited to our objective, since it invoked the stabilized α-carbanions of propyl-substituted nitrogen heterocycles as nucleophiles. While condensation reactions involving methyl azines are well known, much less work has been done on higher alkyl homologues.[7] Likewise, only a limited number of functionalized benzoyl electrophiles have been investigated in reactions with carbanions derived from methyl (or other alkyl) azines.[8] Herein we report that the functionalization tolerated on the benzophenone electrophile depends on the identity of the deprotonated propyl heterocycle with which it is intended to react.

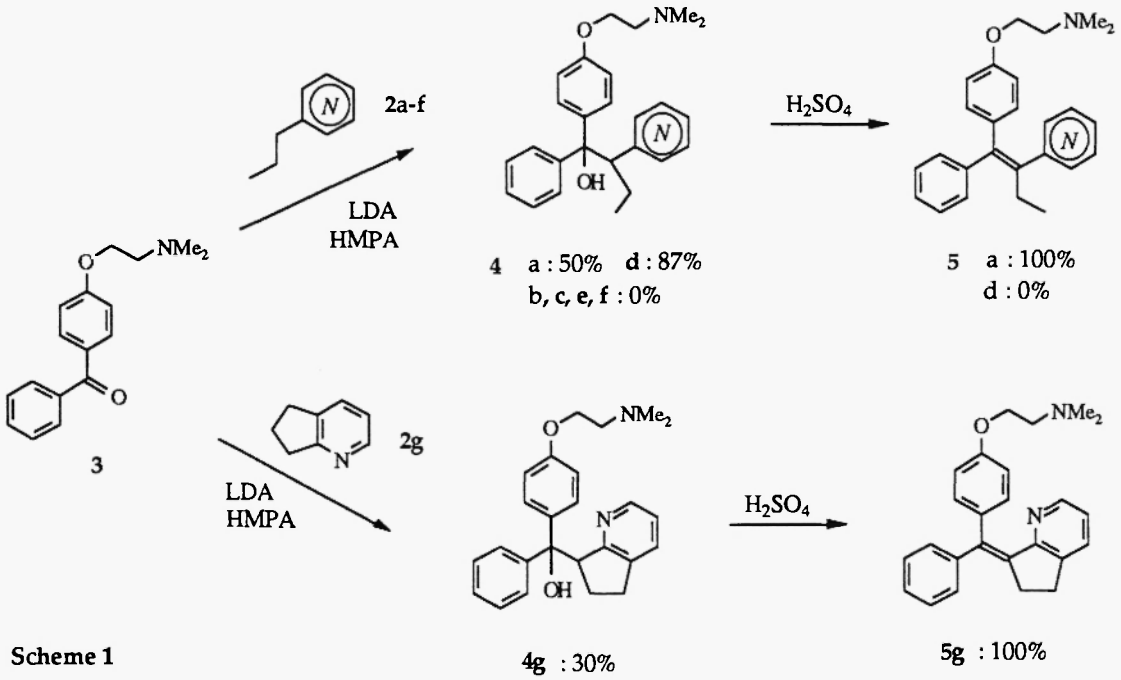




2a **2b** **2c** **2d** **2e** **2f** **2g**

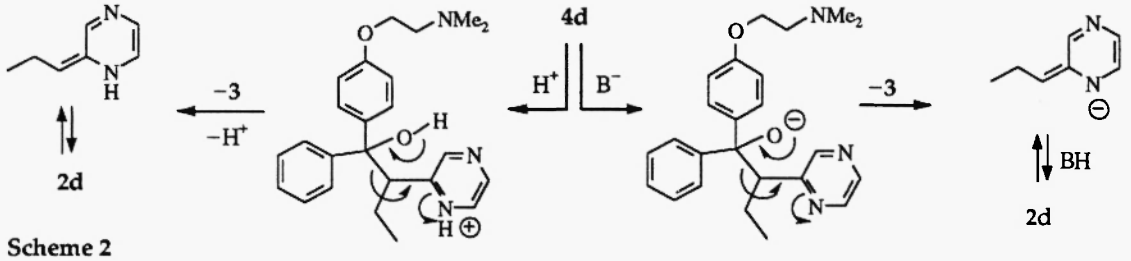
Heterocycles **2a-g** were selected for study. Compounds **2a**, **2d** and **2g** are commercially available, and the other four products were obtained in moderate yields (25-45%) by ethylation of the α-carbanion of the corresponding commercial methyl derivatives, using minor adaptations of literature procedures.[8d,9]

In the first series of experiments, each propyl heterocycle **2** was deprotonated with LDA–HMPA (2 equiv.) in THF at –70°C to give a deep red anion, which was treated with the fully side-chain functionalized benzophenone **3**[10] (Scheme 1). Only **2a**, **2d** and **2g** (the commercial reagents!) gave carbinol condensation products **4** (yields 30-87%); the other heterocyclic anions failed to react with **3**, which was recovered quantitatively from the reaction mixture. Only one regioisomer of **4g** was obtained, which indicated that deprotonation had been achieved regioselectively at the pyridine C-2 methylene substituent, favoured by the resulting charge delocalization onto nitrogen.



Scheme 1

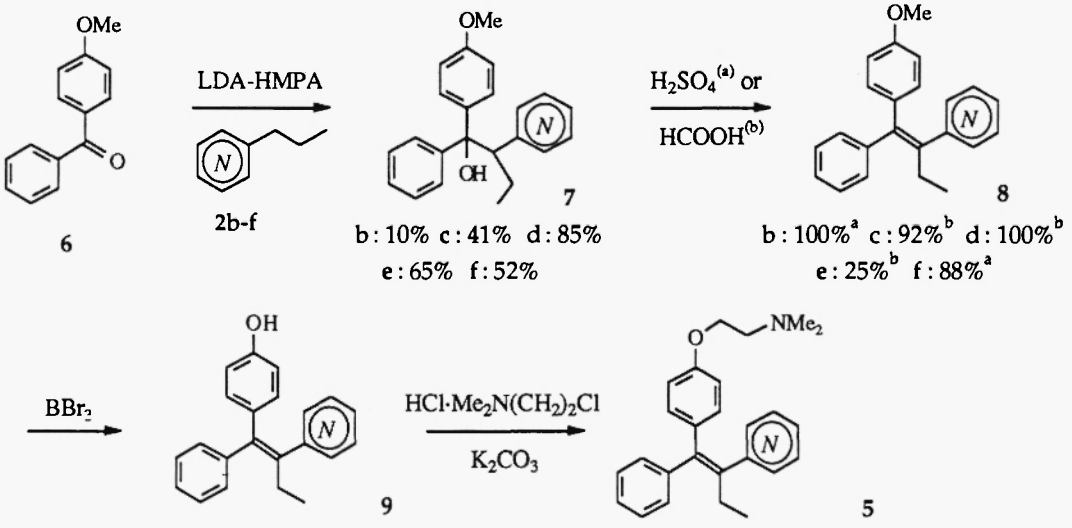
Adducts **4a** and **4g** were dehydrated quantitatively in acid medium (32% H_2SO_4, 3 h, reflux) to complete the very short synthesis of the *C*-ring aza-analogues **5a** and **5g** in 50% and 30% overall yield, respectively. As with most syntheses of Tamoxifen or its analogues, these products were obtained as 50:50 mixtures of *Z* and *E* isomers. In contrast, acid treatment of the pyrazyl adduct **4d**, which had been isolated in good yield (87%) from the condensation reaction, induced a retrocondensation reaction whereby the benzophenone starting material **3** was regenerated. The same phenomenon was observed for **4d** with other acid (HCOOH, AcOH), basic (NaOH-EtOH) or miscellaneous dehydrating media ($POCl_3$-HMPA,[11] DMSO-heat,[12] P_2I_4,[13] DEAD-Ph_3P,[14] Burgss' salt[15]). The likely mecanism for the retrocondensation is shown in Scheme 2; it operates in the case of a 2-pyrazyl but not a 2-pyridyl derivative probably because of the lower energy barrier to loss of aromaticity in the former case. Thermal[8c,16a] and base-catalyzed[16b] retro-condensations have been reported previously for 2-(2-hydroxy-2-arylethyl)pyrazines.



Scheme 2

The use of 3 was successful for only two of the seven heterocycles studied, and it was therefore necessary to use a benzophenone electrophile with a less-developed side chain. In this second approach, the carbanions of 2b-f were treated with the commercial 4-methoxy-benzophenone 6, this time to give the required carbinols 7b-f in variable yields (Scheme 3). Predictably, the poorest yield (10%) was obtained for the heterocycle with the least-easily generated carbanion, i.e. the 3-pyridyl derivative 7b, and to achieve even this low yield, a combination of LDA/BuLi was required as the base. Dehydration of the carbinols (H_2SO_4 or HCOOH, 3h, reflux) gave the olefins 8b-f in good yields (88-100%), except for the 4-pyrimidine derivative, which underwent a competing retrocondensation process analogous to that observed for 4d, resulting in a lower yield of olefin 8c (25%). Nonetheless, all five required olefins were obtained by this approach, and were isolated as 50:50 mixtures of *Z* and *E* isomers. It was noteworthy that the 2-pyrazyl derivative 7d gave no trace of a retrocondensation reaction, in contrast with 4d. Overall, these results were gratifying, given the literature precedent for destructive retrocondensation reactions of 2-(2-hydroxy-2-arylethyl)diazines, particularly those in which the alcohol is tertiary.[8c,16,17]

The basic side chain was introduced by a two-step procedure (Scheme 3). Demethylation using boron tribromide (CH_2Cl_2, 15h, 20°C) proceeded in good yield (70-100%) to give phenols 9b-f which were alkylated (30-83% yield) with (chloroethyl)dimethylamine hydrochloride in the presence of potassium carbonate (DMF, 5h, 110°C) to furnishing the target molecules 5b-f. The 50:50 isomeric ratio remained constant during these procedures, except in the case of the 2-pyrazyl derivative; BBr_3 treatment of the 50:50 *Z*:*E*-8d sample gave phenol 9d in a 75:25 *Z*:*E* ratio, and these proportions remained unchanged in the alkylation step.[18] Triarylethylenes, including Tamoxifen itself, are known to be succeptible to acid-catalyzed isomerization, and the acidity of the BBr_3 reagent should be easily sufficient to permit equilibration; however it is not clear why a 75:25 ratio should be preferred in the case of 9d but not for any other.



Scheme 3

In conclusion, propyl substituted nitrogen heterocycles are efficiently deprotonated at the α-position but react with the highly functionalized benzophenone **3** in only a few cases; the less functionalized benzophenone **6** is a more convenient electrophile, and its side-chain can be developed after the condensation reaction and usually efficient dehydration. A series of C-ring aza-analogues of Tamoxifen has thus been prepared, by either the direct or indirect route.[19] The biological activity of these compounds is under evaluation and will be reported elsewhere.

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