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New efficient pathway for the synthesis of 3-aminoestrone

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Abstract—3-Aminoestrone, a non-natural C-18 steroid, was synthesized by the classical and by a new efficient pathway, the latter using benzophenone imine as an ammonia equivalent in the palladium(0)-catalysed amination of estrone-triflate. This methodology circumvents the problems encountered when applying the classical pathway, the poor yield, high reactional temperature and weak purity.

3-Aminoestrone (**3**) is a versatile precursor of a number of biologically active compounds used for the treatment of hormono-sensitive diseases such as prostate and breast cancers.[1,2] The first report of the biological activity of 3-aminoestrone (**3**), 3-aminoestradiol[3] (**4**) and their derivatives was made by Schwenk and Gold[4,5] who found a large spectrum of activity, such as antiandrogenic, antigonadotropic, estrogenic and pituitary gonadotropin inhibitory activities. Lately, Li and Selcer reported[6,7] and patented[8–10] a new class of non-estrogenic estrone sulfatase inhibitors, composed of the mono and bis trifluoromethyl-sulphonamide, trifluoroacetamide or carbamoyl-amide derivatives of 3-aminoestrone. At the same time, Potter and Woo[11] reported the synthesis, and biological properties of estrone-3-sulphamide as an inhibitor of estrone sulfatase. Moreover, 3-aminoestrone has also been used as a steroidal synthon in the preparation of inhibitors of certain steroidogenic enzymes, type 3 and type 5 of 17β-hydroxysteroid dehydrogenases,[12] and in the synthesis of 3-selenocyanato estrone, a potential estrogen receptor scanning agent.[13] Unfortunately, compounds **3** and **4** are not commercially available, and the classical synthesis method has some disadvantages. So it is desirable to have a simple and efficient method for the preparation of **3**. In addition to a slightly improved classical pathway, we now report a new pathway for an efficient and simple synthesis of 3-aminoestrone, starting from commercially available estrone (Scheme 1).

Keywords: amination; 3-aminoestrone; aminosteroids; steroids; Girard reagent.

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The classical pathway

This already known sequence involves three steps using the general phenols conversion procedure to the corresponding anilines.[14–17] In the first step, the 4-aryloxy-2-phenyl-quinazoline (**1**) was obtained in high yield (98%) by the condensation of a deprotonated estrone with the commercially available 4-chloro-2-phenylquinazoline (AM-ex-OL®) in diglyme. It is also possible to use K_2CO_3 in acetone,[17] but the reaction time and the workup are much longer. The second and the key step of this pathway is a thermally induced rearrangement of quinazoline **1** to a 3-aryl-2-phenyl-4(3*H*)-quinazolinone (**2**). In our case, the thermal rearrangement involved a C-18 steroid moiety migrating from an oxygen to a nitrogen atom. This type of rearrangement was first observed by Tschitschibabin and Jeletzky[18] and bears a formal resemblance to the Chapman rearrangement of aryl-*N*-arylbenzimidates to *N*,*N*-diarylbenzamides.[19] This mechanism of thermal rearrangement involves an intramolecular nucleophilic displacement of the incipient oxygen by the imine nitrogen in a four-membered transition state. We optimized the parameters of this thermal rearrangement and the best yield (91%) was obtained at 350°C and 5 h of heating time. The third and the last step is a basic hydrolysis of quinazolinone **2**, which forms an amidine intermediate. This one is considerably more resistant to further hydrolysis. Acidic hydrolysis of this intermediate amidine forms the hydrochloride salt of 3-aminoestrone (**3**) in 48% yield and 2-phenyl-4*H*-3,1-benzoxazin-4-one as a by-product. Unfortunately, the overall yield for these three steps is only 43%, and the purity of 3-aminoestrone (**3**) is low (generally near 70%), the major impurity being 3-aminoestradiol (**4**). Furthermore,

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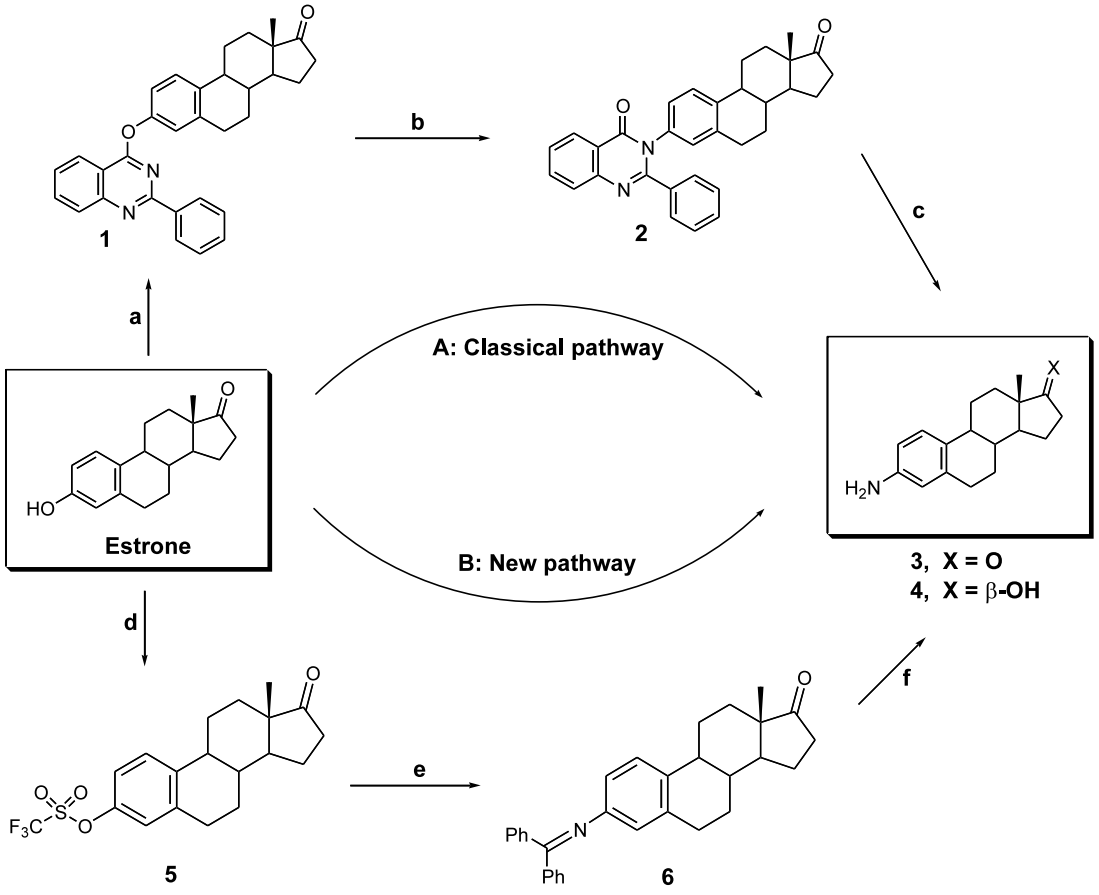

Scheme 1. The classical (**A**) and the new pathway (**B**) for the synthesis of 3-aminoestrone (**3**) from estrone. *Reagents and conditions*: (a) NaH, 4-chloro-2-phenylquinazoline, diglyme, reflux (98%); (b) 350°C, heavy mineral oil (91%); (c) i. 10% NaOH sol. in EtOH–H_2O, 4:1, reflux, ii. HCl conc., reflux, iii. NaOH conc. (48%), overall yield for the three steps 43%; iv. purification by Girard T reagent; (d) Tf_2O, 2,6-lutidine, DMAP, CH_2Cl_2, 0°C to rt (93%); (e) benzophenone imine, $Pd_2(dba)_3$, S-(−)-BINAP, Cs_2CO_3, toluene, Schlenk tube, 120°C (74%); (f) cat. HCl, wet THF, rt, (87%); overall yield for the three steps 60%.

because the synthesis was performed in medium scale (15 g product per batch), the purification of the crude product by chromatographic methods was inconvenient. Thus, we applied a very simple and efficient classical chemical method for the purification of 3-aminoestrone, using the commercially available Girard T reagent ((carboxymethyl)trimethylammonium chloride hydrazide).[20,21] By this rapid procedure the purity of the crude 3-aminoestrone was increased from 67 to 96%, as determined by the HPLC method.[22]

The new efficient pathway

Given the low yield and the poor purity of 3-aminoestrone (**3**) obtained through the classical procedure described above, we were interested in finding another procedure, which could eliminate these disadvantages. We thus applied to estrone triflate the palladium(0)-catalysed amination of the aryl-triflate.[23,24] A classical reaction of triflic anhydride with estrone gave in 93% yield estrone-triflate (**5**).[25] To introduce the nitrogen atom at position C-3 of estrone, the commercially available benzophenone imine served as a convenient ammonia equivalent in the palladium(0)-catalysed amination of the estrone-triflate (**5**). We optimized the parameters of this amination reaction to increase the conversion rate. Thus, our best ratio *product* **6**:*starting material* **5** (11:1) was obtained for 3 days of reaction time at 120°C in a Schlenk tube. At lower temperatures and shorter reaction times the conversion is much poorer. The stable trisubstituted imine **6** was isolated in pure form by silica gel flash chromatography and characterized.[26] In the last step, the trisubstituted diphenyl ketimine **6** can be converted to the corresponding 3-aminoestrone (**3**) under a variety of conditions, such as acidic hydrolysis,[27,28] hydrogenolysis with ammonium formate catalysed by Pd/C,[23] or a transamination reaction with hydroxylamine.[29] We applied the acidic hydrolysis of trisubstituted ketimine **6**, and the desired 3-aminoestrone (**3**) was obtained in a very good yield (87%).[30] The overall yield for the three steps is 60%, in comparison with 43% obtained in the classical pathway, outlined in Scheme 1. Also, it should be mentioned that through this new sequence, we obtained a much purer product (92% purity, as determined by HPLC),[22,31] without the presence of 3-aminoestradiol (**4**), which was a major side product in the classical pathway.

In conclusion, we developed a novel strategy for the synthesis of a C-18 aminosteroid. Distinct advantages of our approach over the classical procedure are the easy preparation of estrone-triflate as starting material, and the absence of non-desirable secondary products in its palladium(0)-catalysed amination reaction. The procedure is particularly useful because of its simplicity, the readily available starting materials and ease of reaction conditions, as well as its applicability to the synthesis of other non-natural C-18 aminosteroids, in addition to the biologically relevant 3-aminoestrone. To our knowledge, to date there is no mention in the literature of such an application of this type of palladium(0)-catalysed amination reaction in the case of C-18 steroid triflates.

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22. Reverse-phase C-18 Nova-Pak C18 column (100×40 mm i.d.). Mixture of CH_3CN:MeOH:H_2O/40:35:25 as eluent at a flow rate of 25 mL/min, UV detection at 205 nm.
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26. **Procedure for the synthesis of 6**: In a Schlenk tube purged with argon, $Pd_2(dba)_3$ (27 mg, 3% mol), S-(−)-BINAP (28 mg, 4.5% mol), Cs_2CO_3 (456 mg, 1.4 mmol) in 2 mL toluene were added and stirring began. To the resulting solution, **5** (403 mg, 1 mmol) and benzophenone imine (201 μL, 1.2 mmol) were added and heated at 120°C for 3 days. The dark colour mixture was then cooled to room temperature and diluted with 25 mL Et_2O and filtered over Celite and then evaporated under reduced pressure. The crude solid was purified by silica gel flash chromatography using gradient elution with CH_2Cl_2 to 3% Et_2O/CH_2Cl_2 to afford 32 mg (8%) of starting material **5** and 321 mg (74%) of imine **6** as a yellow solid. Mp 151–153°C. $[\alpha]_D$ +88.80° (*c* 1.00, $CHCl_3$). IR (KBr): 1739 (C=O); 1597 (C=N) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.90 (s, 18-CH_3); 1.30–1.67 (m, 6H); 1.88–2.26 (m, 5H); 2.27–2.38 (m, 1H); 2.50 (dd, $J_1=19.50$ Hz, $J_2=8.45$ Hz, 16β-CH); 2.72–2.81 (m, 6-CH_2); 6.47 (dd, $J_1=8.20$ Hz, $J_2=1.70$ Hz, 2-CH); 6.55 (s, 4-CH); 7.02 (d, $J=8.20$ Hz, 1-CH); 7.09–7.20 (m, 2H); 7.23–7.32 (m, 3H); 7.33–7.53 (m, 3H); 7.72 (d, $J=7.14$ Hz, 2H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 13.86; 21.54; 25.65; 26.48; 29.25; 31.55; 35.82; 38.11; 44.09; 47.95; 50.47; 118.59; 121.86; 125.25; 127.93; 128.14; 129.58; 134.90; 136.56; 139.61; 148.09; 167.93; 220.90 ppm. MS for $C_{31}H_{32}NO$ $[M+H]^+$: 434.40 *m*/*z*.
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30. To a solution of **6** (26 mg, 0.06 mmol) in wet THF (4 mL), one drop of conc. HCl was added (the yellow colour disappears rapidly) and the solution was stirred at room temperature for 1 h. Then, the mixture was poured into CH_2Cl_2 (30 mL) and the organic phase washed with 20% aqueous NaOH (15 mL), H_2O (30 mL), and brine, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The compound was then purified on silica gel by flash chromatography and eluted with hexanes:EtOAc/5:1 to provide 14 mg (87% yield) of compound **3** (aminoestrone).
31. Characteristics of 3-aminoestrone identical to those reported in the literature (Ref. 11).