Synthesis of Heterocyclic Analogues of Tamoxifen as Potential Antiestrogens

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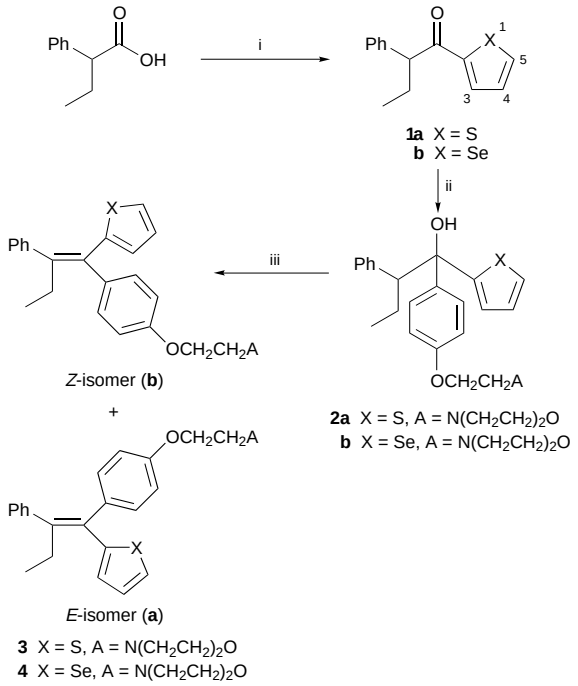
The synthesis of (*E*/*Z*)-1-aryl-2-phenyl-1-(2-thienyl/selenophen-2-yl)but-1-enes, derived from 2-phenyl-1-(2-thienyl/selenophen-2-yl)butan-1-ones, is described; the key steps in the synthesis involve the reaction of the butan-1-ones with 4-(2-morpholinoethoxy)phenyl bromide, followed by dehydration of the resulting carbinols to give the target compounds which are separated by fractional recrystallisation.

Non-steroidal antiestrogens of the triarylethylene type, notably Z-tamoxifen, have been widely used as the first line endocrine therapy drugs for the treatment of estrogen-dependent tumours. It is generally acknowledged that antiestrogens act by competitively inhibiting the binding of estradiol to the estrogen receptor.[1] The clinical efficacy of tamoxifen in the treatment of breast cancer has attracted widespread interest in the synthetic and biological studies of antiestrogens.[2] For this purpose it is essential that only the geometrical isomer of *Z*-configuration is used since the *E*-isomer has unwanted opposing estrogenic properties.[3,4] The separation of the mixture of isomers that results from the synthesis is often not easy and the present separation methods of the *E*–*Z* mixture[5,6] are usually by fractional recrystallisation from a suitable solvent. So far there has been only one report on the synthesis of triarylethylene analogues[7] (1,2-diphenyl-1-pyridylbut-1-enes) in which one of the phenyl groups has been replaced by an aromatic heterocyclic ring (pyridine). An *E:Z* ratio of 1:1 was obtained and only the *Z*-isomer could be separated by fractional recrystallisation.

We report herein the synthesis of (*E*/*Z*)-1-aryl-2-phenyl-1-(2-thienyl/selenophen-2-yl)but-1-enes, derived from 2-phenyl-1-(2-thienyl/selenophen-2-yl)butan-1-ones. It is well known that selenium in the appropriate chemical form and concentration exhibits anticarcinogenic properties in numerous animal tumour model systems.[8]

The methodology used for the synthesis of (*E*/*Z*)-1-aryl-2-phenyl-1-(2-thienyl/selenophen-2-yl)but-1-enes (**3a**, **3b**, **4b**) is depicted in the Scheme. The precursors, 2-phenyl-1-(2-thienyl/selenophen-2-yl)butan-1-ones (**1**), were synthesised by the reaction of thiophene/selenophene with 2-phenylbutyric acid in trifluoroacetic anhydride.[9] The products of electrophilic substitution at positions 2 and 3 of the 5-membered heterocycles can be differentiated by their ^{1}H NMR data.[10] The chemical shifts of **1a**, δ_3 7.71, δ_4 7.05, δ_5 7.56 and coupling constants J_{34} 3.83, J_{35} 1.07, J_{45} 4.92 Hz are consistent with the results reported for 2-substituted thiophenes[10] (δ_3 7.80, δ_4 7.17, δ_5 7.80 and J_{34} 3.74, J_{35} 1.09, J_{45} 5.07 Hz). Similarly the chemical shifts of **1b**, δ_3 7.93, δ_4 7.29, δ_5 8.30 and coupling constants J_{34} 3.98, J_{35} 1.02, J_{45} 5.50 Hz are consistent with the results reported for 2-substituted selenophene[10] (chemical shifts δ_3 8.02, δ_4 7.43, δ_5 8.52 and coupling constants J_{34} 3.96, J_{35} 1.14, J_{45} 5.54 Hz). The reaction of the 2-phenyl-1-(2-thienyl/selenophen-2-yl)butan-1-ones (**1**) with the 4-(2-morpholinoethoxy)phenyl bromide, followed by acid-catalysed dehydration of the tertiary alcohols **2** obtained furnished mixtures of geometric isomers **3** and **4**. The *E*- and *Z*-isomers of the thiophene analogue, **3a** and **3b** (*E:Z* = 1:2), could be separated by recrystallisation from methanol. However, only the *Z*-isomer for the selenium analogue **4b** (*E:Z* = 1:4) could be obtained in the pure state by recrystallisation. It is well known that the geometric isomers of the tamoxifen derivatives can be differentiated by their ^{1}H NMR spectra.[11] Thus the isomers with monosubstituted aromatic rings (1- and 2-phenyl groups) are readily identified on the basis of the chemical shifts of the AB quartet for the protons of the remaining disubstituted aromatic moiety. In the *trans*-isomer (Z-tamoxifen) the AB quartet is usually found at a higher field as a consequence of the combined shielding influence of the two adjacent phenyl rings. On this basis and assuming the heteroaromatic thiophene ring as being equivalent to a phenyl group, compound **3a**, with an AB quartet at δ_H 6.57–6.85 (*J* 8.85 Hz) and other aromatic protons at δ_H 6.95–7.26, can be assigned as the *E*-isomer. Compound **3b**, with an AB quartet at δ_H 6.94–7.23 (*J* 8.72 Hz) and other aromatic protons at δ_H 7.24–7.35, can be assigned as the *Z*-isomer. Further confirmation of these structures was obtained by comparing the chemical shifts of the ethyl and the OCH_2 groups with those reported for the *E*/*Z* isomers of 1-[-4-(2-dimethylaminoethoxy)phenyl]-2-phenyl-1-(4-pyridyl)but-1-ene and other triarylethylene derivatives.[7,12] Thus compound **3a**, showing a triplet at δ_H 1.00 (CH_3), a quartet at δ_H 2.67 (CH_2) and a triplet at δ_H 3.99 (OCH_2), is assigned the *E*-isomer. Compound **3b**, showing a triplet at δ_H 0.87 (CH_3), a quartet at δ_H 2.29 (CH_2) and a triplet at δ_H 4.16 (OCH_2), is assigned the *Z*-isomer. Similarly compound **4** was assigned the *Z*-configuration based on the above results. The struc-



Scheme *Reagents and conditions:* i, TFAA, thiophene/selenophene; ii, *n*-BuLi, *p*-$BrC_6H_4OCH_2CH_2A$, THF, −78 °C; iii, H^+, MeOH, room temperature

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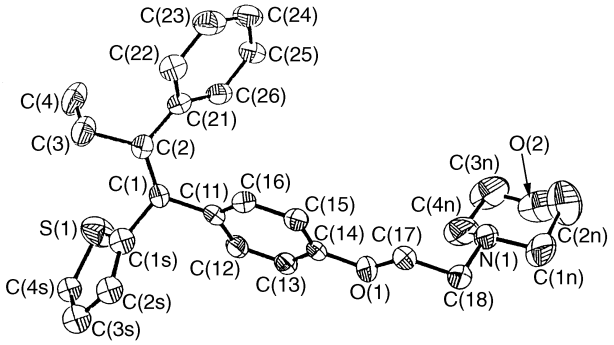

Fig. 1 X-Ray crystal structure of the *E*-isomer of 1[4-(2-morpholino-ethoxy)phenyl]-2-phenyl-1-(2-thienyl)but-1-ene

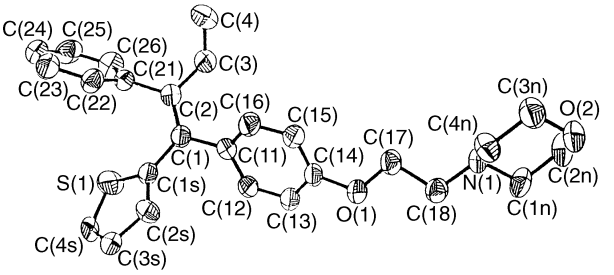

Fig. 2 X-Ray crystal structure of the *Z*-isomer of 1-[4-(2-morpholino-ethoxy)phenyl]-2-phenyl-1-(2-thienyl)but-1-ene

tures of **3a**,**b** have also been confirmed by X-ray diffraction analysis. The X-ray structures of the isomers **3a** and **3b** are shown in Figs. 1 and 2, respectively. The crystal structure of **3a** has monoclinic symmetry. Each asymmetric unit contains one independent molecule. The thiophene ring is disordered to two sets by flipping over around the C(1)—C(1s) bond with site occupancy factors of 0.60 and 0.40. This is possibly due to the free rotation about the C(1)—C(1s) bond. The conformation at the C(1)=C(2) double bond is as follows: (1) bondings at both C(1) and C(2) are planar; (2) the thiophene ring is *cis* to the ethyl group and (3) the $N(CH_2CH_2)_2O$ ring has a chair conformation. The crystal structure of **3b** has orthorhombic symmetry. The thiophene group is again disordered (0.65/0.35). The conformation at the C(1)=C(2) double bond is as follows: (1) bondings at both C(1) and C(2) are planar; (2) the thiophene ring is *trans* to the ethyl group and (3) the $N(CH_2CH_2)_2O$ ring has a chair conformation.

Crystal Data for **3a**.—$C_{26}H_{29}O_2NS$, $M_r = 419.6$, monoclinic, $a = 25.962$ (5), $b = 5.7470$ (10), $c = 31.424$ (6) Å, $\beta = 97.34$ (3)°, $V = 4650$ (2) Å^3, $D_C = 1.199$ mg m^{-3}, $Z = 8$, $F(000) = 1792$, μ(Mo-Kα) = 0.161 mm^{-1}, space group *I*2/*a*.

Crystal Data for **3b**.—$C_{26}H_{29}O_2NS$, $M_r = 419.6$, orthorhombic, $a = 30.604$ (7), $b = 51.461$ (11), $c = 5.8030$ (10) Å, $V = 9139$ (3) Å^3, $D_C = 1.220$ mg m^{-3}, $Z = 16$, $F(000) = 3584$, μ(Mo-Kα) = 0.163 mm^{-1}, space group *Fdd*2.

Crystallographic Analyses.—Data were collected on a Siemens R3m/V diffractometer and structures elucidated by direct methods[13] and refined by full-matrix least-squares analysis.[14] The final *R* value was 0.060 ($R_w = 0.089$) for compound **3a** and 0.039 ($R_w = 0.036$) for compound **3b**.

A preliminary ligand-binding study of compound **3b** (which has the same configuration as E-tamoxifen) on a Molt 4 cell line showed that it had a lower relative binding affinity than Z-tamoxifen. Studies on the bioactivities of the synthetic compounds are in progress.

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Techniques used: IR, ^{1}H NMR, mass spec, elemental analyses, TLC and X-ray diffraction

References: 14

Appendix: Tables of atomic coordinates and equivalent isotropic displacement coefficients, bond lengths and angles, anisotropic displacement coefficients, H-atom coordinates and isotropic displacement coefficients for **3a** and **3b**

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