Na$_2$SO$_4$ (25 mL). The solvents are evaporated and the residue is recrystallized from EtOH to give cis-bropareol; yield: 0.59 g (1.63 mmol, 68%) as a colorless crystalline solid; m.p. 112–113°C (Lit.19 m.p. 112–113.5°C). [Comparison of this product I with an authentic sample11 gave a superimposable 1H-NMR spectrum and a single peak on GLC co-injection (OVI glass column)].

I am grateful to King Abdulaziz City for Science and Technology (KACST) and to Research Center, College of Science, King Saud University, for financial support of this work.

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(11) Bropareol has been previously prepared in our laboratory: Al-Hassan, M.I. J. Organomet. Chem., accepted for publication 1986.

A Single-Step Synthesis of Tamoxifen Using Palladium-Catalyzed Cross-Coupling

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The synthesis of tamoxifen, a biologically active tetrasubstituted olefin, was achieved via palladium-catalyzed cross-coupling of vinylmetal with 2-(4-bromophenoxo)-1-dimethylaminoethane.

Tamoxifen, "1-[4-(2-dimethylaminoethoxy)phenyl]-1,2-di-phenyl-1-butene", is a biologically active tetrasubstituted olefin. The cis-form (1) is not antiestrogenic. On the other hand, the trans-form "Nolvadex" (2) has antiestrogenic activity and is used in the therapy of breast cancer and for the treatment of menstrual disorders.1

\[
\begin{align*}
\text{C}_{6}\text{H}_{5}- & \quad \text{C}_{6}\text{H}_{5} \\
\text{O} & \quad \text{N} \\
\text{CH}_{2} & \quad \text{CH}_{2}
\end{align*}
\]

\[
\begin{align*}
\text{C}_{6}\text{H}_{5}- & \quad \text{C}_{6}\text{H}_{5} \\
\text{N} & \quad \text{C} \\
\text{H}_{2} & \quad \text{CH}_{2}
\end{align*}
\]

We here report a one-step synthesis of tamoxifen (1), (2) via carbometallation of diphenylacetylene (3) followed by C–C cross-coupling of the formed vinylmetal with 2-(4-bromophenoxo)-1-dimethylaminoethane in the presence of a catalytic amount (0.05 equivalent) of tetrakis(triphenylphosphine)-palladium.

Diphenylacetylene (3) was carbometallated in a syn manner2,3 with triethylaluminium in toluene at 90°C to give the cis-

vinylmetal compound which was coupled with 2-(4-bromophenoxy)-1-dimethylaminoethane in the presence of a catalytic amount of palladium(0) to give cis-tamoxifen.4,5 (1) in 35% overall yield.

An attempt to synthesize trans-tamoxifen directly by increasing the carbometallation reaction temperature up to 140°C in order to obtain the trans-vinylmetal intermediate followed by the palladium-catalyzed cross-coupling reaction with 2-(4-bromophenoxo)-1-dimethylaminoethane gave only trace amounts of a mixture of cis- and trans-tamoxifen. Fortunately, isomerization of the previously formed cis-tamoxifen (1) with a catalytic amount of bromine in the presence of light2 gave the antiestrogenic trans-tamoxifen (2) as the major product (65%) and cis-tamoxifen (1) the minor product (35%). Separation of the two isomers is possible either by TLC8 or by recrystallization.9

\[
\begin{align*}
\text{C}_{6}\text{H}_{5}- & \quad \text{C}_{6}\text{H}_{5} \\
\text{O} & \quad \text{N} \\
\text{CH}_{2} & \quad \text{CH}_{2}
\end{align*}
\]

This method appears to be a promising synthesis of tamoxifen and derivatives as compared with the published methods.4,8

cis-Tamoxifen (1):
A solution of the vinylmetal intermediate is prepared by adding a 1 molar solution of triethylaluminium in hexane (15 mL, 15 mmol, 1.2 equiv) to diphenylacetylene (2.23 g, 12.5 mmol, 1 equiv) in toluene (15 mL) at room temperature and stirring the mixture at 90°C for 24 h.

To a separate flask containing tetrakis(triphenylphosphine)palladium (0.72 g, 0.625 mmol, 0.05 equiv) is added 2-(4-bromophenoxy)-1-dimethylaminoethane (3.05 g, 12.5 mmol, 1 equiv) in dry THF (24 mL), and this mixture is added to the vinylmetal solution. The mixture is refluxed for 24 h, cooled to room temperature, quenched with ice-cold 1 normal sulfuric acid (25 mL), and extracted with Et$_2$O (3 x 25 mL). The combined organic layers are washed with saturated NaHCO$_3$ solution and dried (Na$_2$SO$_4$). Evaporation of solvent gives crude 1 as a viscous oil, which is chromatographed to give pure cis-tamoxifen (1) as a colorless crystalline solid; yield: 1.62 g (4.38 mmol, 35%); m.p. 70–72°C (Lit.1 m.p. 72–74°C). [Comparison of product I thus obtained with an authentic sample8 gave superimposable spectra and a single peak upon co-injection by GLC (OVI glass column)].

trans-Tamoxifen (2):
To a solution of cis-Tamoxifen (1; 0.47 g, 1.27 mmol) in Et$_2$O (8 mL) containing a few drops of pyridine is added a 1 molar solution of bromine in CH$_2$Cl$_2$ (0.06 mL, 0.06 mmol, 0.05 equiv) and the mixture is stirred and irradiated with a 100 watt sun lamp for 1 h, followed by the addition of a few drops of pyridine and another 0.05 equiv of bromine in CH$_2$Cl$_2$, and a third portion of both reagents after another hour.

The mixture is then poured into 10% Na$_2$SO$_4$ solution (20 mL), shaken, and separated. The aqueous layer is extracted with Et$_2$O (3 x 20 mL) and the combined organic extracts are washed with ice cold 1 normal H$_2$SO$_4$ (2 x 20 mL) and with saturated NaHCO$_3$ solution (40 mL). After drying (Na$_2$SO$_4$), the solvent is removed to give the crude product (0.42 g, 1.14 mmol, 90% yield) which contains trans-tamoxifen (2) as the major product (65%) and cis-tamoxifen (1) as the minor product (35%). [Comparison of the isomer mixture with authentic samples8 gave superimposable spectra and similar peaks upon co-injection by GLC (OVI glass column)].

Financial support of this work from the King Abdulaziz City for Science and Technology (KACST) is gratefully acknowledged.

Received: 29 December 1986; revised: 11 March 1987
Table. Unsaturated Sulfoxides 2 Prepared

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield (%)</th>
<th>R&lt;sub&gt;t&lt;/sub&gt; Value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Molecular Formula&lt;sup&gt;b&lt;/sup&gt;</th>
<th>IR (CHCl&lt;sub&gt;3&lt;/sub&gt;) ν (cm&lt;sup&gt;-1&lt;/sup&gt;)&lt;sup&gt;1&lt;/sup&gt;</th>
<th>&lt;sup&gt;1&lt;/sup&gt;H-NMR (CDCl&lt;sub&gt;3&lt;/sub&gt;/TMS) δ, J (Hz)</th>
<th>δ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td>52</td>
<td>0.60</td>
<td>C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;20&lt;/sub&gt;OS</td>
<td>3090, 3070, 3010, 2950, 2880, 1640, 1600, 1480, 1445, 1380, 1330, 1270, 1150, 1090, 1070, 1040, 1000</td>
<td>1.56, 1.64 (br. s, 3 H, CH&lt;sub&gt;3&lt;/sub&gt;); 1.7–2.4 (m, 4 H, CH&lt;sub&gt;2&lt;/sub&gt;); 3.1 (m, 1 H, H–3)); 4.6–5.2 (m, 6 H, CH&lt;sub&gt;2&lt;/sub&gt;C=C–C); 6.29 (dd, J = 11.0, 18.0, 1.1 H, H–7)); 7.5 (m, 5 H, C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;)</td>
<td>1.50, 1.56, 1.59 (br. s, 6 H, CH&lt;sub&gt;3&lt;/sub&gt;; 1.8–2.2 (m, 4 H, CH&lt;sub&gt;2&lt;/sub&gt;); 1.9–2.0 (s, 3 H, CH&lt;sub&gt;3&lt;/sub&gt;); 2.9–3.0 (m, 1 H, H–3)); 4.49 (br. d, J = 8, 2 H, H–8); 4.61, 4.70, 4.97 (br. s, 2 H, H–1); 5.25 (br. t, J = 8, 1 H, H–7)); 7.5 (m, 5 H, C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;)</td>
</tr>
<tr>
<td>2b</td>
<td>61</td>
<td>0.34</td>
<td>C&lt;sub&gt;16&lt;/sub&gt;H&lt;sub&gt;22&lt;/sub&gt;OS&lt;sub&gt;2&lt;/sub&gt;</td>
<td>3080, 2990, 2940, 2860, 1735, 1670, 1645, 1485, 1480, 1445, 1380, 1365, 1320, 1270, 1085, 1040, 1000, 955, 910</td>
<td>2c</td>
<td>62</td>
</tr>
<tr>
<td>2d</td>
<td>65</td>
<td>0.57</td>
<td>C&lt;sub&gt;20&lt;/sub&gt;H&lt;sub&gt;26&lt;/sub&gt;OS&lt;sub&gt;2&lt;/sub&gt;</td>
<td>3080, 2990, 2940, 2845, 1705, 1645, 1585, 1485, 1445, 1380, 1350, 1285, 1260, 1140, 1090, 1040, 1000, 910, 870</td>
<td>1.25 (s, 7 H, CH&lt;sub&gt;3&lt;/sub&gt;); 1.49, 1.54, 1.63 (br. s, 6 H, CH&lt;sub&gt;3&lt;/sub&gt;; 1.8–2.2 (m, 8 H, CH&lt;sub&gt;2&lt;/sub&gt;); 2.13 (br. s, 3 H, CH&lt;sub&gt;3&lt;/sub&gt;); 3.0–3.2 (m, 1 H, H–10); 4.13 (q, J = 7, 2 H, CH&lt;sub&gt;2&lt;/sub&gt;); 4.65, 4.73, 5.01 (br. s, 2 H, H–12); 5.0 (m, 1 H, H–6); 5.63 (s, 1 H, H–2)); 7.5 (m, 5 H, C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;5&lt;/sub&gt;)</td>
<td>2.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> Determined using “Silufol UV-254” plates with a bound layer of silica gel (Kavalier, Czechoslovakia); ether/hexane (4:1).  
<sup>b</sup> Satisfactory microanalyses obtained: C ±0.47, H ±0.20, S ±0.39.

product eluted with pentane. The eluant is concentrated under reduced pressure and the residue (0.3 g) is distilled in the presence of hydroquinone (5 mg) to give 4 as a colorless liquid of 98% purity (GLC, <sup>1</sup>HNMR); yield: 0.19 g (51%); b.p. 62–63°C/15 Torr (Lit. , b.p. 54°C/9 Torr); n<sub>D</sub>; 1.5043.

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(1) van Tamelen, E. E. Acc. Chem. Res. 1968, 1, 111.


A One-Step Synthesis of Broparestrol

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A one pot synthesis of broparestrol, a tetrasubstituted olefin with estrogentic activity, was achieved via carboalumination of diphenylacetylene followed by bromination.

Broparestrol [cis-trans mixture of 1-bromo-1,2-diphenyl-2-(4-ethylphenyl)ethylene] (1) is a tetrasubstituted olefin with estrogentic activity, used in dermatology. We here report a one-pot synthesis of broparestrol via carboalumination of diphenylacetylene (2) followed by bromination.

The organoaluminum reagent required for this carboalumination reaction was prepared in situ from 3 equivalents of the corresponding Grignard reagent and 1 equivalent of anhydrous aluminum chloride. Increasing the amount of aluminum chloride lead to the formation of organoaluminum chlorides which did not add to diphenylacetylene. Besides, more than equivalent amounts of Grignard reagent lead to the formation of aluminates which also did not react with diphenylacetylene. No increase in yield was found by using higher reaction temperature, and the reaction failed when stoichiometric amounts of titanocene dichloride were used as in the synthesis of tetrasubstituted olefins. The organoaluminum reagents could also not be replaced by organolithium, Grignard, or organozinc reagents in the presence or absence of titanocene dichloride.

This new procedure for the synthesis of broparestrol compares well with the published methods.

Broparestrol (1): A solution of tris(4-ethylphenyl)aluminum is prepared by adding 4-ethylphenyllimagensium bromide [prepared by refluxing 4-ethylbromobenzene (2.22 g, 12 mmol) with magnesium metal (0.29 g, 12 mmol) and iodine (1 crystal) in anhydrous Et<sub>2</sub>O (6 mL) for 2 h] to anhydrous AlCl<sub>3</sub> (0.48 g, 3.6 mmol) in mesitylene (10 mL). Ether and hexane are distilled off under nitrogen and the resulting mixture is refluxed for 2 h. Then, diphenylacetylene (0.43 g, 2.4 mmol) in mesitylene (3 mL) is added to the above organoaluminum solution and the mixture is refluxed for 24 h. After cooling to −10°C, the solution is diluted with CH<sub>2</sub>Cl<sub>2</sub> (13 mL), solid N-bromosuccinimide (2.14 g, 12 mmol) is gradually added, and stirring is continued for 1 h. The resulting mixture is poured into hexane (50 mL) and washed with saturated aqueous
Table. * Unsymmetrical Sulfides 4 from 1-Alkylthioethaninilum Halides 2 and Alkyl Halides 3

<table>
<thead>
<tr>
<th>Product</th>
<th>X in 1 and 2</th>
<th>Y in 3</th>
<th>Yield* (%)</th>
<th>m.p. (°C) or b.p. (°C/torr)</th>
<th>Molecular Formula/ or Lit. Data</th>
<th>HRMS (70 ev)* m/e (M+1)</th>
<th>1H-NMR (CDCl3/TMS)$^f$ δ, J (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a Br</td>
<td>Br</td>
<td>88</td>
<td>42-43/20</td>
<td>C$<em>8$H$</em>{14}$S (146.2)</td>
<td>146.1125</td>
<td>0.92 [1H, J = 7.4, S(CH$_2$)$_2$CH$_3$]; 0.99 [2H, J = 7.4, S(CH$_2$)$_2$CH$_3$]; 1.40 [2H, J = 7.4, S(CH$_2$)$_2$CH$_3$]; 1.56 (quin, 2H, J = 7.4, S(CH$_2$)$_2$CH$_3$)]; 1.79 [sept, 1H, J = 6.6, S(CH$_2$)$_2$CH$_3$]; 2.39 [2H, J = 6.6, S(CH$_2$)$_2$CH$_3$]; 2.49 [1H, J = 7.4, S(CH$_2$)$_2$CH$_3$]; 4b Br</td>
<td>Cl</td>
</tr>
</tbody>
</table>

---

*a* Reactions were carried out at room temperature for 15 min at the mol ratio 1:1:0.03 for iminium salt, halide, and TBAB.

*b* Yield of pure isolated product based on 1.

*c* Uncorrected, measured with a Yanagimoto apparatus.

*d* Satisfactory microanalyses obtained: C ±0.2, H ±0.2, S ±0.2.

*e* Recorded on a Hitachi M-808B spectrometer.

*f* Obtained on a JEOL GX-400 spectrometer.

---

*aqueous NaOH (50 g) is vigorously stirred at room temperature for 15 min (1.5 h in the cases of 4g, 4k, and 4l) under nitrogen. The organic layer is separated, washed with H$_2$O (3 × 50 mL), dried (Na$_2$SO$_4$), and evaporated. The residual product is distilled under reduced pressure to afford the pure unsymmetrical sulfide 4.*

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An Efficient Synthesis of Unsymmetrical Sulﬁdes Using Liquid-Liquid Phase-Transfer Catalysis

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The reaction between alkyl ethanemidothioate hydroxalides (1-alkythioethanolaminium halides) and organic halides gives unsymmetrical sulﬁdes in good yields under liquid-liquid phase-transfer conditions.

Many methods1–6 for preparing unsymmetrical sulﬁdes (thioethers) have been reported because functionalised organic sulﬁdes are useful intermediates in preparative organic chemistry. Most of the known methods use unpleasantly smelling alkanethiols.

We have earlier reported7 a one-pot nitrile synthesis via a thioimium intermediate by use of benzyl chloride and primary thioureas under liquid-liquid phase-transfer conditions at room temperature. In these reactions, benzyl chloride is quantitatively converted into dibenzyl sulﬁde. In an extension of this work, we report an efﬁcient synthesis of various unsymmetrical sulﬁdes (4) by reaction of 1-alkythioethanolaminium halides (2), hydroxalides of alkyl ethanemidothioates, as a source of alkanethiolate ions, and organic halides (3) under liquid-liquid phase-transfer conditions. The method does not use unpleasantly smelling alkanethiols; it can be utilized to generate a variety of otherwise unavailable thiolate ions under mild conditions and hence a wide range of functionalised organic sulﬁdes can be obtained.

It is known that the reactions of S,S-dialkyl dithiocarbonates with organic halides under liquid-liquid phase-transfer conditions8 and of 1-alkythioalkanaminium salts with organic halides under liquid-solid phase-transfer conditions9 lead to the formation of sulﬁdes. However, the former route requires reaction conditions such as heating a reactant at reﬂux temperature, and the latter gives only moderate yields due to the formation of by-products such as disulﬁdes.

In the present work, 1-alkythioethanolaminium salts (2), freshly prepared (and isolated) from the S-alkylation of thioacetamide with organic halides (1), react with alkyl halides to afford sulﬁdes 4 in a liquid-liquid two-phase system consisting of benzene, aqueous sodium hydroxide, and a catalytic amount of tetrabutylammonium bromide (TBAB). The reactions proceed smoothly at room temperature and are complete within 15 min, except for the reactions of 2 with allyl bromide and with ethyl chloroacetate as alkyl halide 3, the unsymmetrical sulﬁdes 4 being obtained in 77–100% yields. The products 4 are not obtained in the absence of phase-transfer catalyst under otherwise identical conditions.

Since formation of by-products is rarely observed with this method the unsymmetrical sulﬁdes 4 can be easily be isolated in all cases studied.

The attempted use of acyl halides in place of alkyl halides 3 for the synthesis of thio-carboxylic S-esters was unsuccessful due to the preferential formation of N-acetylthioimidates by electrophilic attack of the carbonyl C-atom of the acyl halide on the N-atom of 2. Likewise, the attempted use of 1,4-dihaloalkanes in place of 1 and 3 for the preparation of cyclic sulﬁdes was unsuccessful due to the formation of polymeric sulﬁdes.

1-alkythioethanolaminium Bromide (2, R3 = C6H5CH2, X = Br): Typical Procedure:
Mixing a solution of thioacetamide (3.75 g, 50 mmol) and benzyl bromide (8.55 g, 50 mmol) in CHCl3 (50 mL) is refluxed for 1 h. After cooling, the product is isolated by suction and washed with ether; yield: 11.04 g (90%); m. p. 174–176°C (Lit.10 m. p. 174–176°C). (246.2) found 439.43 4.82 5.75

H-NMR (CDCl3/TMS): δ = 2.75 (s, 3H, CH3); 4.80 (s, 2H, SCHR); 7.31–7.44 (m, 5H arom); 11.78–12.47 (br s, 2H, NH2).

If other alkyl halides used instead of benzyl bromide the product does not crystallize from the mixture, some ether is added.

Unsymmetrical Sulﬁdes 4; General Procedure:
Mixing a mixture of freshly prepared 1-alkythioethanolaminium halide 2 (10 mmol), the organic halide 3 (10 mmol), tetrabutylammonium bromide (TBAB; 97 mg, 0.3 mmol), benzene (50 mL), and 30 wt%
COMMUNICATION

SELECTIVE AROMATISATION OF CYCLOHEXENONE(*)

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Summary — Selective aromatisation of cyclohexenone was achieved via abstraction of an α-proton of 2-cyclohexenone by LDA followed by treatment with phenylselenenylic chloride which gave the corresponding phenol upon oxidation.

A new method for selective aromatisation of cyclohexenones to the corresponding phenols has been developed using organoselenium intermediates. Abstraction of an α-proton of 2-cyclohexenone by secondary amide bases such as lithium disopropylamide (LDA) is kinetically favoured. Electrophilic attack of phenylselenenyl chloride was followed by oxidation of the formed selenide to selenoxide which eliminates the β-proton spontaneously (the β-proton must be cis to selenoxide due to syn elimination) to give 1,4-cyclohexadienone which subsequently isomerises to the corresponding phenol due to aromatic stabilisation.

It was found that oxidation of the selenide with 2 equivalents of m-chloroperbenzoic acid (MCPA) at −15 °C or with 3.5 equivalents of 30% hydrogen peroxide at −15 °C work only after work-up of the formed selenide; however, purification of the crude selenide was not necessary.

According to the literature, the common dehydrogenating agents include sulphur, selenium, a palladium catalyst, a platinum catalyst and several quinones (quinones containing electron-withdrawing substituents such as chloranil, DDQ). Recently, a method of aromatisation of cyclohexenone to benzene by treatment with pyridinium chloride has been described. However, this method works only when certain substituents are present and the product is benzene and not phenol. These alternative methods of aromatisation of cyclohexenone do not give selective aromatisation of cyclohexenone in the presence of other cyclohexene rings, so low yields of the desired product are obtained (such as in the synthesis of steroids and other natural products). Moreover, most of the aromatisation methods need high temperatures (~250 °C) which may induce structure changes in the compounds via rearrangement or affect some substituents, while the newly developed method operates under milder conditions (from −78 °C to room temperature).

EXPERIMENTAL

Cyclohexenone (4.8 g, 1 equiv) in 50 ml of dry tetrahydrofuran (THF) was added slowly to a slight excess of LDA (1.05 equiv) (prepared by adding an equivalent amount of n-butyllithium to dry disopropylamine in dry THF at −10 °C over 10 min) at −78 °C. After keeping the mixture for 10 min at −78 °C, 50 ml of THF solution containing phenylselenyl chloride (10 g, equivalent to LDA or slightly in excess) was then added rapidly (reaction is instantaneous). The resulting solution was washed with an excess of 0.1 N HCl and extracted with diethyl ether. The combined organic layers were washed with saturated sodium chloride solution and dried over anhydrous sodium sulphate. Evaporation of solvents led to a residue which was oxidised either with 2 equivalents of MCPA (powder, 14.67 g) in 50 ml of THF or with 3.5 equivalents of 30% hydrogen peroxide (1.75 mmol) in 50 ml of THF at −15 °C for 0.5 h. The reaction mixture was allowed to warm up to room temperature, acidified with 0.1 N HCl and extracted with diethyl ether. Drying and evaporation of solvents gave a residue which was recrystallised from petroleum ether (b.p. 40-60 °C) to give the corresponding phenol (1) in 55% overall yield (2.59 g, 27.5 mmol). Comparison with an authentic sample gave superimposable spectra and a single peak upon co-injection in gpc (OV1 glass column).

Similarly, starting from bicyclo [4.4.0]-1-decen-3-one, the corresponding phenol (2) was obtained in 50% overall yield.

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