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Simple and Efficient Production of (*Z*)-4-Hydroxytamoxifen, a Potent Estrogen Receptor Modulator

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Abstract: A McMurry coupling reaction and selective crystallization were used to develop a simple and efficient two-step synthesis of (*Z*)-4-hydroxytamoxifen (**2a**). This compound is an active metabolite of tamoxifen, a selective estrogen receptor (ER) modulator widely used to treat breast cancer. The synthesis employed 1,1-bis(4-hydroxyphenyl)-2-phenylbut-1-ene (**1**) as a useful building block.

Estrogen receptors (ER)[1] are members of the superfamily of ligand-modulated nuclear receptors that mediate the actions of steroid hormones, vitamin D, retinoids, and thyroid hormones. ER is activated in vivo when bound by naturally occurring estrogens such as 17β-estradiol (E_2) (Figure 1). Ligand binding results in a conformation change that alters the transcriptional activities of ER.[2] This in turn leads to specific changes in the activity of gene networks that regulate the female reproductive system, bone mineral density, lipid homeostasis, central nervous system, and cardiovascular function.[2]

In addition to regulating these physiological processes, estrogen also plays a central role in stimulating breast cancer growth. Therefore, the use of estrogen for its positive physiological effects can result in deleterious side effects.[3] As a result, there is considerable interest in the therapeutic profile of a unique class of drugs known as selective ER modulators (SERMs).[4,5] These drugs are useful because they can prevent breast cancer growth by acting as ER antagonists in the breast while maintaining the therapeutic property of agonists in other tissues.

(*Z*)-Tamoxifen ((*Z*)-2-[4-(1,2-diphenyl-1-butenyl)phenoxy]-*N*,*N*-dimethylethanamine) (Figure 1) is a first-generation SERM that is currently approved by the Food and Drug Administration and is widely used to treat estrogen-dependent breast cancers.[6] An active metabolite of (*Z*)-tamoxifen is (*Z*)-4-hydroxytamoxifen ((*Z*)-1-[4-(2-dimethylaminoethoxy)phenyl)]-1-(4-hydroxyphenyl)-2-phenylbut-1-ene (Figure 1), which binds to ER with 8-fold higher affinity than tamoxifen.[7] Only the *Z* isomer has the required antiestrogenic activity; the (*E*)-4-hydroxytamoxifen has only about 5% of its affinity for the ER.[8] Since (*Z*)-4-hydroxytamoxifen readily equilibrates into a *Z*/*E* mixture,[8] there is considerable need for the discovery of a straightforward synthesis that produces high yields of the pure *Z* isomer without loss by isomerization.

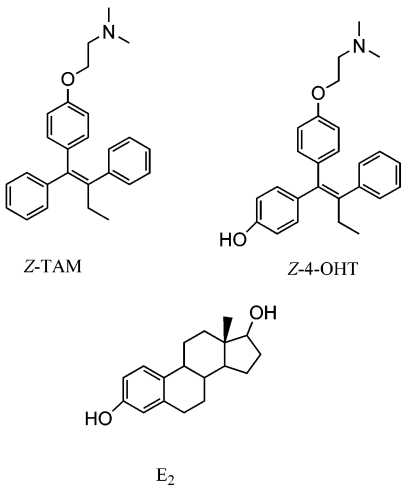
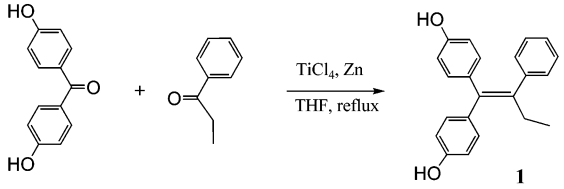


FIGURE 1. Chemical structures of (*Z*)-tamoxifen, (*Z*)-4-hydroxytamoxifen, and E_2.

SCHEME 1



We reviewed numerous synthetic strategies including stereoselective syntheses of tamoxifen and 4-hydroxytamoxifen.[9−14] Gust and co-workers[7] synthesized 1,1-bis-(4-hydroxyphenyl)-2-phenylalkene analogues. The published methods for the preparation of these compounds, including 1,1-bis(4-hydroxyphenyl)-2-phenylbut-1-ene (**1**), are long and proceed in five steps[7,15] starting with 1-(4-methoxyphenyl)-2-phenylethan-1-one which is obtained by a Friedel−Crafts acylation of phenylacetyl chloride and anisole. The products were reacted with the appropriate alkyl bromides under the influence of potas-

(1) Karnik, P. S.; Kulkarni, S.; Liu, X. P.; Budd, G. T.; Bukowski, R. M. *Cancer Res.* **1994**, *54*, 349.
(2) McCague, R.; Leclercq, G. *J. Med. Chem.* **1987**, *30*, 1761.
(3) *Cancer Facts and Figures*; American Cancer Society: New York, 1997.
(4) Katzenellenbogen, B. S.; Katzenellenbogen, J. A. *Science* **2002**, *295*, 2380.
(5) Shang, Y.; Myles, B. *Science* **2002**, *295*, 2465.
(6) Jordan, V. C. *J. Med. Chem.* **2003**, *46*, 883.
(7) Lubczyk, V.; Bachmann, H.; Gust, R. *J. Med. Chem.* **2002**, *45*, 5358.
(8) Robertson, D. W.; Katzenellenbogen, J. A.; Long, D, J.; Rorke, E. A.; Katzenellenbogen, B. S. *J. Steroid Biochem.* **1982**, *16*, 1.
(9) Al-Hassan, M. I. *Synth. Commun.* **1989**, *19*, 1619.
(10) Gauthier, S.; Mailhot, J.; Labrie, F. *J. Org. Chem.* **1996**, *61*, 3890.
(11) Detsi, A.; Koufaki, M.; Calogeropoulou, T. *J. Org. Chem.* **2002**, *67*, 4608.
(12) McCague, R. *J. Chem. Res., Synop.* **1986**, 58.
(13) Foster, A. B.; Jarman, M.; Leung, O. T.; McCague, R.; Leclercq, G.; Devleeschouwer, N. *J. Med. Chem.* **1985**, *28*, 1491.
(14) Olier-Reuchet, C.; Aitken, D. J.; Bucourt, R.; Husson, H, P. *Tetrahedron Lett.* **1995**, *36*, 8221.
(15) Dodds, E. C.; Golberg, L.; Lawson, W.; Robinson, R. *Proc. R. Soc. London Ser. B* **1939**, *127*, 140.

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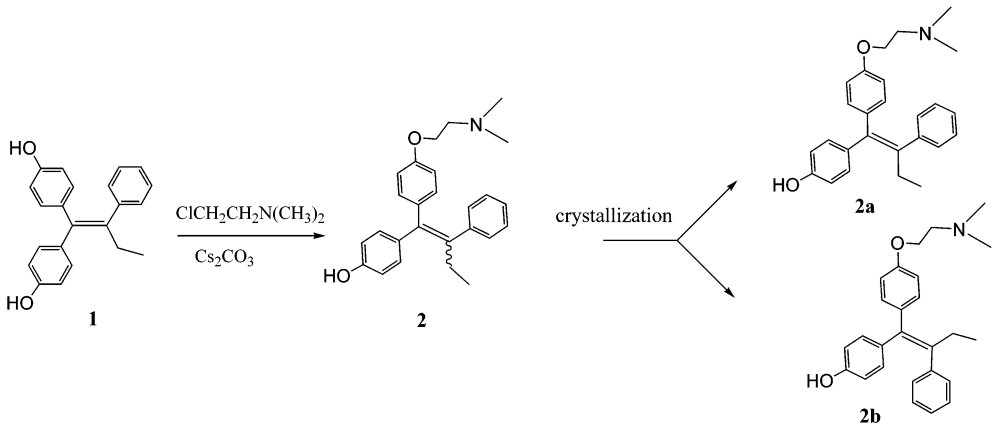
SCHEME 2



sium *tert*-butyl alcoholate to obtain the C2-alkyl-substituted intermediates. These intermediates were reacted with 4-methoxyphenylmagnesium bromide by the Grignard reaction to yield the corresponding carbinols, which were dehydrated by either phosphoric acid or hydrobromic acid in THF. The methoxy groups were then converted to hydroxyls substituted on the benzene rings with BBr_3 to afford the 1,1-bis(4-hydroxyphenyl)-2-phenylalkenes.

The McMurry reaction has been used by several groups as a key step in the stereoselective synthesis of (*Z*)-4-hydroxytamoxifen.[10,11] This reaction is a version of titanium-mediated reductive coupling in which $TiCl_4-Zn$ serves as the reductant to completely remove oxygen with the formation of an alkene.[16] Gauthier et al.[10] used the McMurry reaction as the main step in their synthesis of (*Z*)-4-hydroxytamoxifen. They made the monopivaloate derivative of 4,4′-dihydroxybenzophenone and reacted it with propiophenone under McMurry reaction conditions to produce a 14:1 *E*/*Z* ratio in favor of the desired triarylethylene. The unprotected phenol was then alkylated and the pivaloyl ester was removed as the final step. More recently, Calogeroupoulou et al.[11] employed benzyl monoprotected 4,4′-dihydroxybenzophenone to couple with propiophenone under McMurry conditions. The resulting two isomeric triarylethylenes were converted to corresponding perfluorotolyl ethers, which were separated. These protective groups were then removed by sodium methoxide in DMF, and the final step was a mild debenzylation without *E*/*Z* isomerization.

We wanted to develop a more efficient procedure for the synthesis of (*Z*)-4-hydroxytamoxifen by minimizing the number of steps requiring protection groups. To do so, we utilized 1,1-bis(4-hydroxyphenyl)-2-phenylbut-1-ene (**1**) as an efficient synthetic precursor and we improved the yield of this precursor from inexpensive starting materials. The successful synthetic route is shown in Schemes 1 and 2.

Scheme 1 consists of a McMurry reductive coupling between 4,4′-dihydroxybenzophenone and propiophenone in the presence of zinc and titanium tetrachloride in dry THF under reflux conditions. This results in 91% yield of 1,1-bis(4-hydroxyphenyl)-2-phenylbut-ene (**1**) in a small-scale (0.5 g) synthesis. The same reaction expanded to a 4-g scale resulted in an 87% yield.

In Scheme 2, we couple **1** directly with 2-(dimethylamino)ethyl chloride hydrochloride using a known method[10] and obtain an equimolar mixture of the geometrical isomers of 4-hydroxytamoxifen (**2**). In previous strategies for the synthesis of 4-hydroxytamoxifen, separation of the isomers was a difficult task involving preparative TLC or HPLC. We explored the possibility of using selective crystallization to simplify the separation. Several solvents were tested including methanol, ethanol, 2-propanol, butanol, pentanol, and ethyl acetate. We were ultimately able to separate the geometric isomers as follows: (*Z*)-4-hydroxytamoxifen was crystallized from hexanol (49% yield) and (*E*)-4-hydroxytamoxifen from methanol (41% yield). The geometry of (*Z*)-4-hydroxytamoxifen and (*E*)-4-hydroxytamoxifen was confirmed by ^1H NMR using CD_3OD as a solvent. (*Z*)-4-Hydroxytamoxifen has upfield NMR signals of the 2-dimethylaminoethoxy chain protons compared to the corresponding (*E*)-4-hydroxytamoxifen.[10] Interestingly, if $CDCl_3$ is used as a solvent, the samples undergo a facile isomerization to a mixture of (*Z*/*E*)-4-hydroxytamoxifen. Presumably, the isomerization is caused by acid catalysis or by a bimolecular oxidative−reductive reaction that might result in a single bond rotation.[17−19] Further studies are required to confirm the mechanism underlying this observation.

In summary, the above one-pot synthesis of 1,1-bis(4-hydroxyphenyl)-2-phenylbut-1-ene (**1**) by the McMurry reaction and coupling with 2-(dimethylamino)ethyl chloride hydrochloride gave a 1:1 *Z*/*E* ratio of 4-hydroxytamoxifen and the *Z*- and *E*-isomers were effectively separated by selective crystallization. Thus, our novel strategy allows for the efficient production of (*Z*)-4-hydroxytamoxifen with two simple synthetic steps followed by crystallization. While many other approaches to 4-hydroxytamoxifen have been reported, our procedure offers a simpler pathway suitable for large-scale industrial production.

Experimental Section

General Procedures. Organic reagents were purchased from commercial suppliers unless otherwise noted and were used

(16) McMurry, J. E.; Fleming, M. P. *J. Org. Chem*. **1976**, *41*, 896.

(17) Katzenellenbogen, J. A.; Carlson, K. E.; Katzenellenbogen B. S. *J. Steroid Biochem*. **1985**, *22*, 589.

(18) Airy, S. C.; Sinsheimer, J. E. *Steroids*. **1981**, *38*, 593.

(19) Winkler V. W.; Nyman, M. A.; Egan, R. S. *Steroids*. **1971**, *17*, 197.

without further purification. All solvents were analytical or reagent grade. All reactions were carried out in flame-dried glassware under argon or nitrogen. Melting points were determined and reported automatically by an optoelectronic sensor in open capillary tubes and were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured at 500 and 125 MHz, respectively, using $CDCl_3$ or CD_3OD as the solvents and tetramethylsilane (Me_4Si) as the internal standard. Liquid column chromatography was carried out under moderate pressure by using columns of an appropriate size packed and eluted with appropriate eluents. All reactions were monitored by TLC on precoated plates (silica gel HLF). TLC spots were visualized either by exposure to iodine vapors or by irradiation with UV light. Organic solvents were removed in a vacuum by rotary evaporator. Elemental analyses were performed by Desert Analytics, Tucson, AZ.

1,1-Bis(4-hydroxyphenyl)-2-phenylbut-1-ene (1). To a stirred suspension of zinc powder (2.0 g, 0.031 mol) in dry THF (20 mL) was added dropwise $TiCl_4$ (1.5 mL, 0.014 mol) under Ar, at −10 °C. When the addition was complete, the mixture was warmed to room temperature and then refluxed for 2 h. To the cooled suspension of the titanium reagent was added a solution of 4,4′-hydroxybenzophenone (0.5 g, 0.0023 mol) and propiophenone (1.0 g, 0.0074 mol) in dry THF (40 mL) at 0 °C, and the mixture was refluxed in the dark for 2 h. After being cooled to rt, the reaction mixture was quenched with 10% aqueous potassium carbonate (30 mL) and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Flash column chromatography (8:2 hexanes/EtOAc) afforded **1** (0.66 g, 91%) as a white solid: mp 200.6 °C; ^{1}H NMR ($CDCl_3$) δ 7.17−7.10 (m, 7H), 6.86 (d, 2H), 6.75 (d, 2H), 6.49 (d, 2H), 4.65 (s, 1H), 4.43 (s, 1H), 2.49 (q, 2H), 0.92 (t, 3H); ^{13}C NMR ($CDCl_3$) δ 157.0, 156.2, 143.8, 141.0, 139.5, 136.0, 135.6, 132.6, 131.2, 130.5, 128.6, 126.0, 115.7, 115.0, 29.5, 13.8. Anal. Calcd for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.23; H, 6.58.

***(E,Z)*- 1-[4-(2-Dimethylaminoethoxy)phenyl]-1-(4-hydroxyphenyl)-2-phenylbut-1-ene ((*E,Z*)-4-Hydroxytamoxifen) (2).** A solution of 1,1-bis(4-hydroxyphenyl)-2-phenylbut-1-ene (**1**) (0.45 g, 0.0014 mol) in DMF (5 mL) was treated with Cs_2CO_3 (1.06 g, 0.0033 mol) and heated in an oil bath at 70−80 °C for 10 min. The resulting suspension was treated with 2-(dimethylamino)ethyl chloride hydrochloride (0.75 g, 0.005 mol) in a small portion over a 15 min period and stirred for 1.5 h. After being cooled to rt, the reaction mixture was poured into saturated ammonium chloride (10 mL) and extracted with ethyl acetate (4 × 10 mL). The combined organic phase was washed with brine (4 × 10 mL), dried, and concentrated in vacuo. Flash chromatography (9:1 CH_2Cl_2/MeOH) afforded **2** (0.35 g, 64%); triturating (petroleum ether−diethyl ether) afforded **2** as a white solid: mp 143.3 °C, as a 1:1 mixture of (*E*)-**2b**/(*Z*)-**2a** isomers; ^{1}H NMR ($CDCl_3$) δ 7.06−7.15 (m, 7H), 6.80 (d, 2H), 6.69 (d, 2H), 6.35 (d, 2H), 4.07 (t, 1H), 3.91 (t, 1H), 2.79 (t, 1H), 2.69 (t, 1H), 2.49 (q, 2H), 2.38 (s, 3H), 2.33 (s, 3H), 0.89 (t, 3H).

***(Z)*-1-[4-(2-Dimethylaminoethoxy)phenyl]-1-(4-hydroxyphenyl)-2-phenylbut-1-ene ((*Z*)-4-Hydroxytamoxifen) (2a).** Crystallization of the white solid (**2**) with a 1:1 *Z*/*E* ratio (10 mg) from warm hexanol (0.1 mL) gave white crystals (**2a**) (4.9 mg): mp 143.6 °C (lit.[10] mp140−143 °C); ^{1}H NMR (CD_3OD) δ 7.08−7.01 (m, 5H), 7.02 (d, 2H), 6.96 (d, 2H), 6.71(d, 2H), 6.52 (d, 2H), 3.91 (t, 2H), 2.66 (t, 2H), 2.44 (q, 2H), 2.25 (s, 6H), 0.87 (t, 3H); ^{13}C NMR (CD_3OD) δ 156.5, 155.4, 142.6, 139.7, 137.9, 136.0, 133.0, 131.6, 130.9, 128.8, 126.9,114.3, 64.5, 59.1, 45.7, 29.8, 13.8. Anal. Calcd for $C_{26}H_{29}NO_2$: C, 80.59; H, 7.54; N, 3.61. Found: C, 80.63; H, 7.52; N, 3.44.

***(E)*-1-[4-(2-Dimethylaminoethoxy)phenyl]-1-(4-hydroxyphenyl)-2-phenylbut-1-ene ((*E*)-4-Hydroxytamoxifen) (2b).** Crystallization of the white solid (**2**) with a 1:1 *Z*/*E* ratio (10 mg) from warm methanol (0.1 mL) gave white crystals (**2b**) (4.1 mg): mp 157.8 °C (lit.[10] mp155−157°C); ^{1}H NMR (CD_3OD) δ 7.08−7.05 (m, 7H), 6.89 (d, 2H), 6.58 (d, 2H), 6.35 (d, 2H), 4.07 (t, 2H), 2.75 (t, 2H), 2.42 (q, 2H), 2.32 (s, 6H), 0.85 (t, 3H); ^{13}C NMR (CD_3OD) δ 158.9, 156.4, 144.1, 141.8, 139.7, 137.9, 135.9, 133.0, 131.6, 130.8, 128.8, 126.9, 115.1, 66.6, 59.1, 45.8, 29.8, 13.9. Anal. Calcd for $C_{26}H_{29}NO_2$: C, 80.59; H, 7.54; N, 3.61. Found: C, 80.90; H, 7.55; N, 3.87.

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