Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters
Tetrahedron Letters 47 (2006) 1631–1635

Short-step synthesis of droloxifene via the three-component coupling reaction among aromatic aldehyde, cinnamyltrimethylsilane, and β-chlorophenetole

Yoshiyuki Sano and Isamu Shiina*

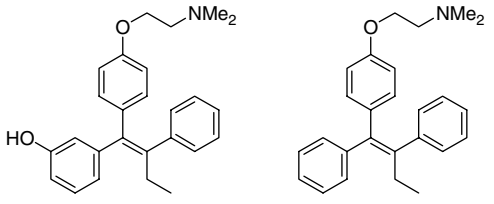
Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, 1-3, Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

Received 10 November 2005; revised 17 December 2005; accepted 21 December 2005
Available online 19 January 2006

Abstract—A short-step route for the preparation of droloxifene has been established via the novel three-component coupling reaction among 3-pivaloyloxybenzaldehyde, cinnamyltrimethylsilane, and β-chlorophenetole, the successive installation of the side-chain part, and the base-induced migration of the double bond. The present synthesis of tetra-substituted ethylene moieties is a widely applicable strategy for producing a variety of SERMs (selective estrogen receptor modulators) and SARMs (selective androgen receptor modulators), such as tamoxifen, raloxifene, and other compounds that can lead to new drugs.

1. Introduction

Droloxifene (**1**), an estrogenic and anti-estrogenic active compound, is known as one of the tamoxifen derivatives used for the treatment and prevention of recurrence of women's breast cancer.[1] It is also expected that **1** might be a therapeutic drug candidate for postmenopausal and senile osteoporosis, because **1** has a similar selective activity to the estrogen receptor like that of 17β-estradiol.[2]



1 **1′**

Figure 1. Droloxifene (**1**), tamoxifen (**2**).

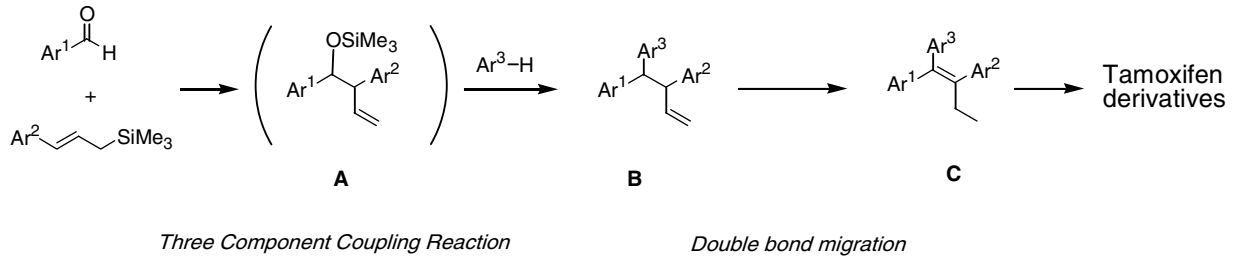
Two general synthetic pathways for the preparation of **1** have been reported according to the widely used tamoxifen synthesis;[3] namely, (i) one of them includes the formation of the double-bond functionalities by a dehydration reaction of the resulting tertiary alcohols, which are generated by the Grignard reaction of benzyl phenyl ketones with aromatic nucleophiles,[4] while (ii) the other employs the reductive coupling reaction of unsymmetrical aromatic carbonyl compounds using low-valent titanium species to form the desired tetra-substituted double bond.[5] Although several approaches classified into the above two typical strategies for the synthesis of **1** have been developed, multiple synthetic steps are required to produce **1** and its derivatives (Fig. 1).

Recently, we have established the novel three-component coupling reaction, which can afford 3,4,4-trisubstituted butenes (**B**), through the allylation reaction of aromatic aldehydes and successive Friedel–Crafts type alkylation of the resulting homoallyl silyl ethers (**A**) with aromatic nucleophiles ($\mathbf{Ar}^3$–**H**) in the presence of a Lewis acid catalyst (Scheme 1).[6] Furthermore, we have shown that the synthetic intermediates (**B**) generated via the three-component coupling reaction among benzaldehyde, cinnamyltrimethylsilane, and anisole could be converted into tamoxifen, an anti-cancer drug widely used all over the world, followed by the successive double-bond migration reaction to form **C** corresponding to the basic skeleton of tamoxifen.

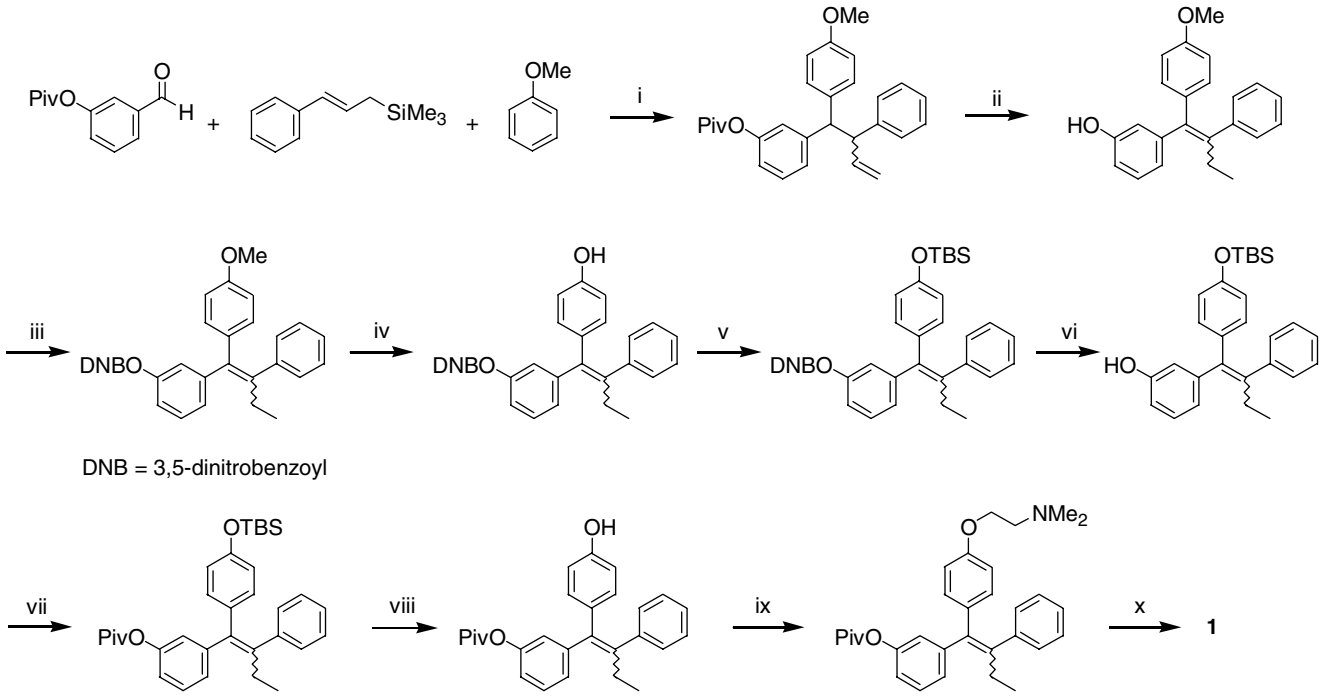
Initially, we planned to apply this strategy to the synthesis of **1** as shown in Scheme 2. The three-component coupling reaction among 3-pivaloyloxybenzaldehyde,

* Corresponding author. Tel.: +81 3 5228 8263; fax: +81 3 3260 5609; e-mail: shiina@ch.kagu.tus.ac.jp

0040-4039/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.12.117



Scheme 1. A novel synthetic pathway to produce tamoxifen derivatives via the three-component coupling reaction.



Scheme 2. A preliminary synthetic route for the preparation of droloxifene using the three-component coupling reaction. Regents and conditions: (i) $HfCl_4$ (1 equiv), TMSOTf (0.5 equiv), 72%; (ii) *t*-BuOK, DMSO, 89%; (iii) 3,5-dinitrobenzoyl chloride, NaH, DMF, 85%; (iv) BBr_3, CH_2Cl_2, 89%; (v) TBSOTf, pyridine, 99%; (vi) K_2CO_3, MeOH, 86%; (vii) Pivaloyl chloride, NaH, DMF, 74%; (viii) KF, HBr, DMF, quant.; (ix) *N*,*N*-dimethylaminoethyl chloride, K_2CO_3, acetone–H_2O, 46%; (x) MeLi, THF, 61%.[5]

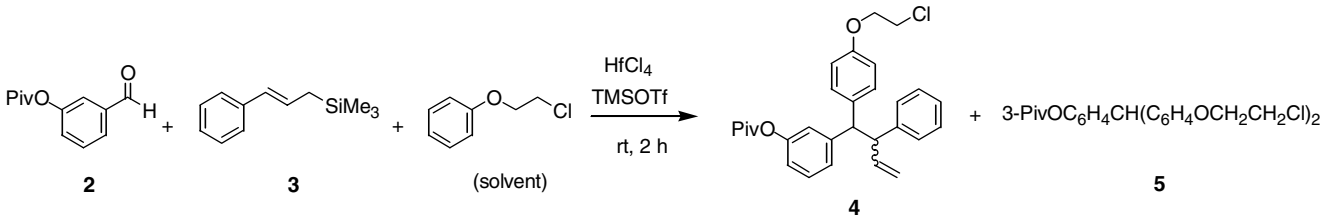
cinnamyltrimethylsilane, and anisole proceeded as well as the case for the synthesis of tamoxifen, and the corresponding 3,4,4-trisubstituted butene was obtained in a satisfactory yield. However, the chemoselective installation of the *N*,*N*-dimethylaminoethyl side chain to the framework of **1** required a complicated roundabout pathway due to the existence of a deprotecting step for cleaving the *O*-methyl group that originated from the anisole moiety under the severe reaction conditions.

After the preliminary study of the synthesis of **1** using the three-component coupling reaction among 3-pivaloyloxybenzaldehyde, cinnamyltrimethylsilane, and anisole, it was again planned to use β-chlorophenetole (2-chloroethyl phenyl ether) as a second nucleophile instead of anisole to produce the intermediary homoallyl silyl ethers (**A**) in order to decrease the total steps for the synthesis of **1** from the starting materials. It seems that the chloroethoxy group will be easily converted to the corresponding dialkylaminoethoxy group by treatment with a secondary dialkylamine before carrying out the olefin migration promoted by the basic catalyst. This synthetic approach would be practically applicable for the effective production of novel tamoxifen-type drugs, that is, the so-called SERMs (selective estrogen receptor modulators) and SARMs (selective androgen receptor modulators) having activities against hormonal disturbances. In this letter, a new and concise method for the preparation of **1** using the improved three-component coupling reaction among an aromatic aldehyde, cinnamyltrimethylsilane, and β-chlorophenetole by the promotion of Lewis acid catalysts, and the successive double-bond migration reaction promoted by a basic catalyst is described.

2. Results and discussion

First, the amount of the co-catalyst was screened for the reaction of 3-pivaloyloxybenzaldehyde with cinnamyltri-

Table 1. The three-component coupling reaction among 3-pivaloyloxybenzaldehyde, cinnamyltrimethylsilane, and β-chlorophenetole using $HfCl_4$ and TMSOTf as catalysts



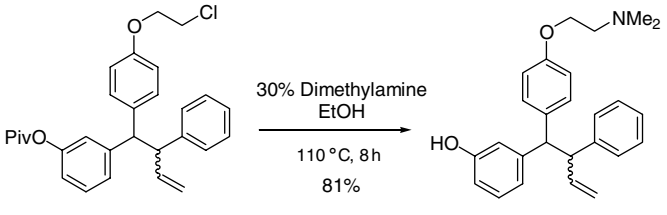
2 **3** (solvent) **4** **5**

Entry	Catalyst (equiv)		Mol. ratio of **2**/**3**	Yield of **4**/%	Yield of **5**/%
	$HfCl_4$	TMSOTf			
1	1.0	0	1/1	12	Trace
2	1.0	0.05	1/1	26	21
3	1.0	0.1	1/1	27	15
4	1.0	0.2	1/1	21	23
5	1.0	0.3	1/1	19	26
6	1.0	0.5	1/1	Trace	30
7	1.0	0.1	1/1.5	38	5
8	1.0	0.1	1/2	43	18

methylsilane in β-chlorophenetole solvent to optimize the suitable ratio of TMSOTf to $HfCl_4$. When no co-catalyst was added to the reaction system, a large amount of starting 3-pivaloyloxybenzaldehyde was recovered and the corresponding homoallyl alcohol derived from the intermediate alkyl silyl ether was mainly obtained (Table 1, entry 1). In entries 5 and 6, a large amount of triarylmethanes (**5**), which were produced from a 1 molar amount of 3-pivaloyloxybenzaldehyde and 2 molar amounts of β-chlorophenetole, was preferentially produced by the addition of 30–50 mol % of the co-catalyst to the reaction mixture because the aldehyde was over-activated by TMSOTf. On the other hand, the desired three-component coupling product (**4**) was obtained in a better yield when 10 mol % of TMSOTf was additionally used with a stoichiometric amount of $HfCl_4$ as shown in entry 3. The yield of the desired three-component coupling product was finally improved up to 43% using a twofold amount of cinnamyltrimethylsilane to 3-pivaloyloxybenzaldehyde (entry 8). It was also revealed that all of the reaction afforded nearly stoichiometric amounts of the *syn*- and *anti*-diastereomers of the 3,4,4-trisubstituted butenes by careful analysis using HPLC–MS; however, these compounds could be converted to the identical 1,1,2-trisubstituted butene after the double-bond migration. Therefore, it is not required to separate these compounds in our short-step strategy for the synthesis of **1**. Furthermore, no more than 10% of the *o*-isomers originated from the nucleophilic substitution of β-chlorophenetole with the intermediary homoallyl silyl ethers were also detected by the HPLC–MS analysis.

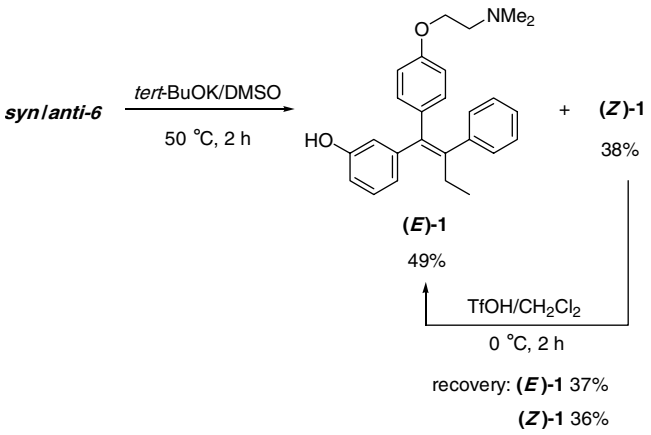
Next, the *N*,*N*-dimethylamination was successfully accomplished by heating the three-component coupling product (**4**) with 30% dimethylamine in ethanol at 110 °C in a sealed vessel for 8 h to produce a mixture of the *syn*- and *anti*-3,4,4-trisubstituted butenes having the side chain (**6**) in good yield (Scheme 3). The pivaloyl protective group was simultaneously removed under these reaction conditions. Although the *syn*- and *anti*-isomers are separable at this stage by silica gel column chromatography, further purification was not carried out since it is unnecessary to separate these compounds for preparing the identical 1,1,2-trisubstituted butene, a precursor of **1**, by the double-bond migration in the next step.

Finally, the desired (*E*)-**1** was prepared in 49% yield from the 3,4,4-trisubstituted butenes by treating with an excess amount of *t*-BuOK in DMSO at 50 °C via the base-catalyzed double-bond migration reaction established for the synthesis of tamoxifen (Scheme 4).[6] Although this olefin transformation was accompanied by the formation of a nearly stoichiometric amount of (*Z*)-**1** with the formation of (*E*)-**1**, the isomers are easily



***syn/anti*-4** ***syn/anti*-6**

Scheme 3. Side-chain installation to form the precursor of droloxifene using dimethylamine in ethanol.



Scheme 4. Double-bond migration reaction to form droloxifene and isomerization between (*E*)-**1** and (*Z*)-**1**.

separable by silica gel chromatography or fractional crystallization of the corresponding acid salts. Furthermore, each isomer could be easily transformed into a mixture of (*E*)-**1** and (*Z*)-**1** again by the treatment with trifluoromethanesulfonic acid (TfOH) in CH_2Cl_2. Therefore, the combined yield of (*E*)-**1** could be increased to nearly 70% involving this isomerization procedure.

3. Conclusion

Thus, we developed a new synthetic route for producing droloxifene (**1**) in only three steps; that is, the sequential one-pot allylation and Friedel–Crafts type alkylation using Lewis acid catalysts (43%), installation of the side chain (81%) and the base-induced double-bond migration (>49%). This synthetic strategy seems to serve as a new and practical pathway to prepare not only droloxifene, but also the other SERMs and SARMs, including the estrogen-dependent breast cancer agents such as tamoxifen and its derivatives.

4. Typical experimental procedure for the three-component coupling reaction among 3-pivaloyloxybenzaldehyde, cinnamyltrimethylsilane, and β-chlorophenetole (Table 1, entry 8)

To a suspension of $HfCl_4$ (490 mg, 1.53 mmol) in β-chlorophenetole (1 mL), trimethylsilyl trifluoromethanesulfonate (34.0 mg, 0.153 mmol) was added as a co-catalyst, then a solution of (*E*)-cinnamyltrimethylsilane[7] (583 mg, 3.06 mmol) and 3-pivaloyloxybenzaldehyde (316 mg, 1.53 mmol) in β-chlorophenetole (1 mL) was slowly added at room temperature under argon atmosphere. The mixture was stirred for 2 h, then poured into a saturated $NaHCO_3$ solution (50 mL) and extracted with Et_2O (30 mL × 1, 10 mL × 2). The combined organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by silica gel column chromatography (hexane–ethyl acetate 9:1) and successive thin-layer chromatography (toluene–hexane 17:1) to afford the corresponding coupling product (**4**) as a viscous colorless oil (308 mg, 43%, the ratio of *p*/*o* is >9:1, the ratio of *syn*/*anti* is ca 6:4 from HPLC analysis).

5. Typical experimental procedure for *N*,*N*-dimethylamination of 4 (Scheme 3)

A solution of the product obtained from the former reaction (421 mg, 0.909 mmol) in 30% dimethylamine-ethanol (3 mL) was heated for 8 h at 110 °C in a sealed vessel. The reaction mixture was concentrated under reduced pressure and the residue was purified by TLC (chloroform–methanol 9:1) to afford the amination product (**6**) as a colorless oil (285 mg, 81%).

6. Typical experimental procedure for double-bond migration (Scheme 4)

A solution of **6** (199 mg, 0.512 mmol) in dimethylsulfoxide (1 mL) was added to a solution of *t*-BuOK (373 mg, 3.32 mmol) in dimethylsulfoxide (1 mL), and stirred at 50 °C for 2 h. The reaction mixture was poured into a saturated NH_4Cl solution (30 mL), then extracted with ethyl ether (30 mL × 3). The combined organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by TLC (ammoniacal chloroform–methanol 19:1) to give the (*E*)-droloxifene and (*Z*)-droloxifene as colorless solids (97.4 mg, 49%; 74.5 mg, 38%, respectively).

7. Typical experimental procedure for *E*/*Z* isomerization (Scheme 4)

To a solution of (*Z*)-droloxifene (73.0 mg, 0.158 mmol) in CH_2Cl_2 (2 mL), trifluoromethanesulfonic acid (140 μL, 1.58 mmol) was added at 0 °C under argon atmosphere, and then stirred at the same temperature for 2 h. A saturated $NaHCO_3$ solution (20 mL) was added to the reaction mixture, then extracted with CH_2Cl_2 (10 mL × 3). The organic phase was dried (Na_2SO_4) and concentrated. The residue was purified by TLC (ammoniacal chloroform–methanol 19:1) to afford (*E*)-droloxifene (26.7 mg, 37%). (*Z*)-droloxifene was also recovered (26.4 mg, 36%).

References and notes

1. (a) Hasmann, M.; Löser, R.; Kohr, A.; Seibel, K. *Onkologie* **1994**, *17*, 22; (b) Biedermann, E.; Löser, R.; Hasmann, M. *Onkologie* **1994**, *17*, 17; (c) Rauschning, W.; Pritchard, K. I. *Breast Cancer Res. Treat.* **1994**, *31*, 83; (d) Gradishar, W. J.; Jordan, V. C. *J. Clin. Oncol.* **1997**, *15*, 840.
2. (a) Ke, H. Z.; Chen, H. K.; Simmons, H. A.; Pirie, C. M.; Ma, Y. F.; Jee, W. S. S.; Thompson, D. D. *Bone* **1995**, *16*, 99S; (b) Chen, H. K.; Ke, H. Z.; Jee, W. S. S.; Ma, Y. F.; Pirie, C. M.; Simmons, H. A.; Thompson, D. D. *J. Bone Miner. Res.* **1995**, *10*, 1256; (c) Ke, H. Z.; Chen, H. K.; Qi, H.; Pirie, C.; Simmons, H. A.; Ma, Y. F.; Jee, W. S. S.; Thompson, D. D. *Bone* **1995**, *17*, 491; (d) Chen, H. K.; Ke, H. Z.; Lin, C. H.; Ma, Y. F.; Qi, H.; Crawford, D. T.; Pirie, C. M.; Simmons, H. A.; Jee, W. S. S.; Thompson, D. D. *Bone* **1995**, *17*, 175S; (e) Ke, H. Z.; Chen, H. K.; Simmons, H. A.; Qi, H.; Crawford, D. T.; Pirie, C. M.; Chidsey-Frink,

K. L.; Ma, Y. F.; Jee, W. S. S.; Thompson, D. D. *Bone* **1997**, *20*, 31.
3. For the examples of tamoxifen synthesis recently reported. See: Zhou, C.; Larock, R. C. *J. Org. Chem.* **2005**, *70*, 3765, and references cited therein.
4. (a) Ruenitz, P. C.; Bagley, J. R.; Mokler, C. M. *J. Med. Chem.* **1982**, *25*, 1056; (b) Schickaneder, H.; Loeser, R.; Grill, H. Eur. Patent EP 54168, 1982; *Chem. Abstr.* **1982**, *97*, 215730; (c) Loeser, R.; Grill, H.; Schickaneder, H.; Seibel, K. Ger. Patent DE 3425413, 1986; *Chem. Abstr.* **1986**, *105*, 42468; (d) Foster, A. B.; Jarman, M.; Leung, O.-T., ; McCague, R.; Leclercq, G.; Devleeschouwer, N. *J. Med. Chem.* **1985**, *28*, 1491; (e) Chen, Y.; Xia, P.; Zhang, Q.; Zheng, Y.-h.; Xia, Y.; Yang, Z.-y. *Acta Pharm. Sinica* **2000**, *35*, 902.
5. Gauthier, S.; Sancéau, J.-Y.; Mailhot, J.; Caron, B.; Cloutier, J. *Tetrahedron* **2000**, *56*, 703.
6. (a) Shiina, I.; Suzuki, M.; Yokoyama, K. *Tetrahedron Lett.* **2002**, *43*, 6395; (b) Shiina, I.; Suzuki, M.; Yokoyama, K. *Tetrahedron Lett.* **2004**, *45*, 965.
7. Andreini, B. P.; Carpita, A.; Rossi, R.; Scamuzzi, B. *Tetrahedron* **1989**, *45*, 5621.