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Short-step synthesis of tamoxifen and its derivatives via the three-component coupling reaction and migration of the double bond

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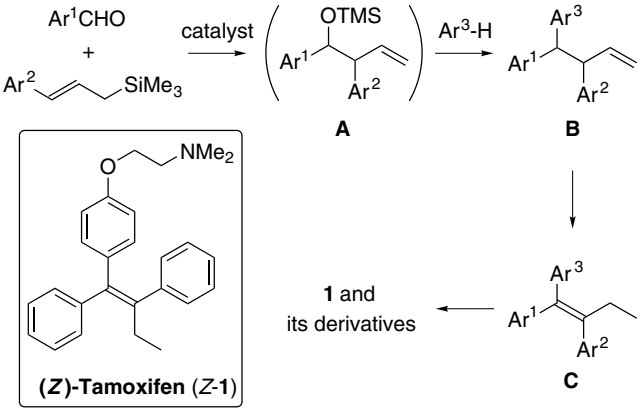
Abstract—The anti-tumor agent, tamoxifen, is easily synthesized by the successive allylation of benzaldehyde and the Friedel–Crafts alkylation reaction of anisole with the intermediary homoallyl silyl ethers, followed by the migration of the double bond to form the desired tetra-substituted ethylenes. Several derivatives of tamoxifen are also produced according to a similar synthetic strategy.

(*Z*)-Tamoxifen (*Z*-**1**), an estrogenic antagonist, has been used as an effective anti-tumor drug for estrogen-dependent breast cancer.[1] The synthesis of the tetra-substituted alkene core structure has been a challenging topic for synthetic chemists.

There are two types of general methods for the construction of the basic skeleton of **1** and its derivatives. One of them includes the formation of the double bond by a dehydration reaction of the corresponding tertiary alcohols or by the reductive coupling of two aromatic ketones.[2,3] In the other synthesis, ethylene moieties are constructed during the early synthetic stage and successive coupling of the olefins with metallated aromatics is carried out in the presence of a transition metal catalyst such as titanium, palladium, and nickel species to produce the desired substituted olefins.[4–8]

On the other hand, it seems possible to generate tetra-substituted alkenes **C**, the precursors of **1**, from the corresponding 3,4,4-trisubstituted butenes **B** by the migration of the double bond as shown in Scheme 1. According to this new and alternative synthetic strategy of **1**, the development of an effective method for the synthesis of various 3,4,4-trisubstituted butenes **B** is required.

The preparation of the key intermediates **B** could be realized by the acid catalyzed substitution of **A** with aromatic compounds (Ar^3H) because several substituted diarylmethanes were synthesized by the Friedel–Crafts alkylation reaction of aromatic nucleophiles such as anisole with benzyl silyl ethers.[9] Additionally, we recently established a new and useful method for the synthesis of 4,4-disubstituted butenes, which correspond to **B** missing the Ar^2 group, via the three-component coupling among aldehydes, allyltrimethylsilanes, and aromatic compounds.[10] During this synthesis, both the allylation forming alkyl silyl ethers and successive Friedel–Crafts alkylation with the formed alkyl silyl ethers were performed under acidic conditions. Therefore, it is anticipated that an effective method for the synthesis of **C** could be determined by the three-component coupling among aromatic aldehydes, cinnamyltrimethylsilanes,



Scheme 1. A novel synthetic pathway of tamoxifen (**1**).

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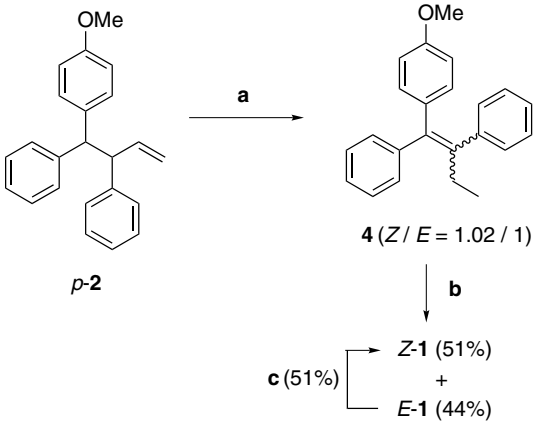
and aromatic nucleophiles followed by a double bond migration.

We now report a new sequential method for the synthesis of various trisubstituted butenes **B** via the allylation of aldehydes to give the corresponding **A**, and successive Friedel–Crafts alkylation reaction of aromatic compounds with the formed **A**. Furthermore, the effective and concise total synthesis of **1** and some tamoxifen analogues through **C** employing this method is also described.

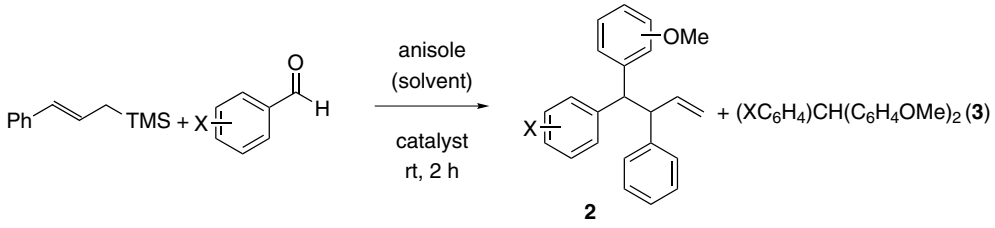
First, benzaldehyde and cinnamyltrimethylsilane were chosen as substrates to optimize the reaction conditions for the three-component coupling reaction (Table 1). Unfortunately, $HfCl_4$ is not very effective for the reaction of benzaldehyde with cinnamyltrimethylsilane in anisole solvent because the reactivity of cinnamyltrimethylsilane is lower compared to that of allyltrimethylsilane (entry 1). When $Cl_2Hf(OTf)_2$ or $Hf(OTf)_4$ was used for the reaction, a regioisomeric mixture of the corresponding triarylmethanes **3** was only obtained in 51% or 23% yield (entry 3 or 4). Second, TMSCl or TMSOTf was added to the reaction mixture as a co-catalyst in order to increase the activity of $HfCl_4$ as shown in entries 5–9.[11] It was then proved that the use of a mixture of a stoichiometric amount of $HfCl_4$ and 50 mol% TMSOTf is the most effective combination for this reaction, and the desired trisubstituted butenes **2** ((*o*-)/(*p*-) = 30/70) were produced in a total of 57% yields via a one-pot operation (entry 8). 3-Pivaloyloxybenzaldehyde was also utilized for this synthesis by the promotion of the combined catalyst to form the corresponding butenes in good yield. The three-component coupling reaction among the halogenated aromatic aldehydes, cinnamyltrimethylsilane, and anisole, smoothly proceeded in the presence of $HfCl_4$ without a co-catalyst since the reactivity of these substituted aromatic aldehydes is higher than that of benzaldehyde.



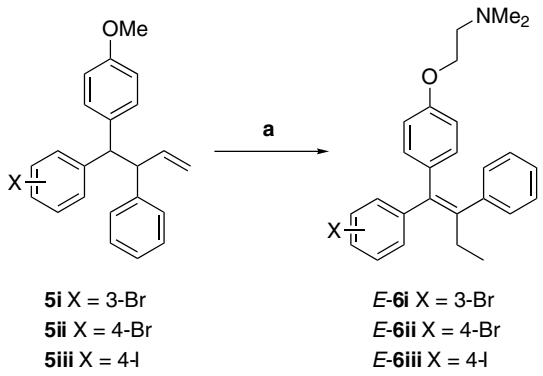
Scheme 2. Reagents and conditions: (a) ^{t}BuOK, DMSO, rt, 15 min (96%); (b) (1) BBr_3, CH_2Cl_2, −78 °C, 2 h (98%); (2) NaH, $ClCH_2CH_2NMe_2$, DMF, 50 °C, 30 min (51% of *Z*-**1**, 44% of *E*-**1**); (c) TfOH, CH_2Cl_2, 0 °C, 3 h (51% of *Z*-**1**, 46% of *E*-**1**).

The migration of the double bond in *p*-**2** was then eventually tried under several reaction conditions (Scheme 2). It was found that ^{t}BuOK is a quite effective catalyst for the desired reaction,[12] and a geometric mixture of the tetra-substituted alkenes **4** was afforded in nearly quantitative yield. The deprotection of **4** and alkylation of the phenol moieties were carried out and then an isomeric mixture of the target compounds **1** was obtained. After separation of these isomers by preparative TLC,[2b,13] pure *Z*-**1** was synthesized in only four steps from the benzaldehyde. Furthermore, the resulting *E*-**1** was isomerized to enrich the desired *Z*-isomer ($Z/E = 1.1/1$) according to the reported procedure.[2c,14]

Table 1. Three-component coupling reaction among aromatic aldehydes, cinnamyltrimethylsilane, and anisole using a Lewis acid



Entry	X	Catalyst	Yield of **2**/%	(*o*-)/(*p*-)	Yield of **3**/%
1	H	$HfCl_4$	36	30/70	20
2	H	$Cl_3Hf(OTf)$	49	30/70	15
3	H	$Cl_2Hf(OTf)_2$	0	—	51
4	H	$Hf(OTf)_4$	0	—	23
5	H	$HfCl_4$+TMSCl (0.5)	39	27/73	14
6	H	$HfCl_4$+TMSCl (1)	33	27/73	11
7	H	$HfCl_4$+TMSOTf (0.2)	37	31/69	6
8	H	$HfCl_4$+TMSOTf (0.5)	57	30/70	4
9	3-OPiv	$HfCl_4$+TMSOTf (0.5)	72	19/81	11
10	3-Br	$HfCl_4$	73	19/81	18
11	4-Br	$HfCl_4$	70	9/91	14
12	4-I	$HfCl_4$	73	16/84	7



Scheme 3. Reagents and conditions: (a) (1) ^{t}BuOK, DMSO, rt, 15 min (**i**; 68%, **ii**; 89%, **iii**; 85%); (2) BBr_3, CH_2Cl_2, −78 °C, 2 h (**i**; 94%, **ii**; 92%, **iii**; 95%); (3) NaH, $ClCH_2CH_2NMe_2$·HCl, DMF, 50 °C, 8–13 h (**6i**; 82% (46% of *E*-**6i**, 36% of *Z*-**6i**), **6ii**; 88% (45% of *E*-**6ii**, 43% of *Z*-**6ii**), **6iii**; 95% (44% of *E*-**6iii**, 51% of *Z*-**6iii**)), (4) *Z*-**6**, TfOH, CH_2Cl_2, 0 °C, 3 h (**6i**; 88% (44% of *E*-**6i**, 44% of *Z*-**6i**), **6ii**; 89% (46% of *E*-**6ii**, 43% of *Z*-**6ii**), **6iii**; 87% (42% of *E*-**6iii**, 45% of *Z*-**6iii**)).

Using this transformation and the second separation of the geometrical isomers, *Z*-**1** was obtained in 28% total yield from the starting substrate (benzaldehyde).

Finally, the substituted tamoxifens were also prepared in good yields by a similar protocol as shown in Scheme 3. Successive double bond migrations took place again to afford the desired tetra-substituted olefins in good yields. The usual treatments of these isomers with BBr_3 and $NaH/ClCH_2CH_2NMe_2$ gave the 3- or 4-halogenated tamoxifen relatives (*E*-**6i**–**iii**)[15] in 23%, 34%, and 32% total yields, respectively, from the corresponding aromatic aldehydes. It is noted that these halogenated derivatives might not be efficiently prepared by the transition metal coupling methodology since aryl halide parts competitively react to form by-products under the reaction conditions.[5]

Thus, we developed a new pathway for the synthesis of tamoxifen and its derivatives via the successive allylation of aromatic aldehydes and Friedel–Crafts alkylation, followed by migration of the double bond. This method seems to be a practical and useful way for the preparation of other tamoxifen analogues since various substances are easily applicable for the first three-component coupling.

A typical experimental procedure is described for the three-component coupling reaction among benzaldehyde, cinnamyltrimethylsilane, and anisole: to a suspension of hafnium tetrachloride (75.6 mg, 0.236 mmol) and trimethylsilyl trifluoromethanesulfonate (26.2 mg, 0.118 mmol) in anisole (1.2 mL) at 0 °C was added a solution of cinnamyltrimethylsilane (57.9 mg, 0.283 mmol) and benzaldehyde (25.0 mg, 0.236 mmol) in anisole (1.2 mL). The reaction mixture was stirred for 2 h at room temperature and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with diethyl ether, and the organic layer was washed with brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford 4-(4-methoxyphenyl)-3,4-diphenylbut-1-ene (42.4 mg, 57%) as a colorless oil.

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