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Synthesis of substituted aryl enol ethers

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ABSTRACT

A facile route toward substituted aryl diarylvinyl ethers **4** is developed from CuI-mediated cross-coupling reaction of substituted phenols **2** with diarylvinyl bromides **3** in the presence of various bidentate-based ligands in DMF. Skeleton **3** is prepared by Yan's bromomethylenation of diarylketones **1** with $CHBr_3$–$TiCl_4$–Mg in the co-solvent of DME and CH_2Cl_2. The synthetic route obtains moderate yields from the one-step operation and the key structure of **4k** is confirmed by X-ray crystallographic analysis. The CADD docking experiments of **4k** have been included.

Introduction

The novel design and synthesis of conformationally multi-functionalized cyclic vinyl ethers (e.g., 2,3-diarylbenzofurans) have attracted considerable attention from both the synthetic and medicinal chemistry communities.[1,2] Acyclic aryl enol ethers (aryl diarylvinyl ethers) have received considerable attention for their use in organic synthesis.[3] Aryl vinyl ethers are important building blocks in organic synthesis and have been applied as monomers in material chemistry.[4] Compared with the structure of diarylbenzofuran and aryl diarylvinyl ethers, the motif of aryl vinyl ether is a common skeleton (red, green, and blue), as shown in Scheme 1.

There are two differences. One is the formation of a cyclic ring (brown), and the other is the C2/C3 position of the aryl group (black). On the contrary, Tamoxifen (Nolvadex®) and Afimoxifene (Mifegyne®), with specific pharmaceutical activities have exhibited a triarylethylene skeleton.[5] Based on the observation for structural frameworks of aryl diarylvinyl ethers and Tamoxifen, one C3 aryl substituent (black-brown) is retained and the other C3 aryl group (blue) is changed to a C2 position. For linkage of aryloxy-conjugated styrene (red-green), the exchange of the ArO—C2 bond and OAr—C2 bond is achieved by a 180° rotation of the aryloxy nucleus.

In addition, the C(sp^2)–O vinylation of multi-functionalized phenols with vinyl halides or triflates by using transition-metals as a catalyst (e.g., Cu,[6] Pd,[7] Ir,[8] Cu/Ni[9]) has been developed for one-pot construction of vinyl enol ethers. Among these examples, the Cu(I)-mediated vinylation reaction with various ligands is the major synthetic route. Due to specific pharmaceutical interest concerning the arrangement of substitution patterns of aryl substituents, we developed an efficient synthetic route to prepare functionalized aryl diarylvinyl ethers **4** via the CuI-mediated C—O bond formation of substituted phenols **2** with 1,1-diarylvinyl bromides **3** in the presence of 2,2′-bipyridine (a bidentate-based ligand), as shown in Scheme 2.

Results and discussion

Yan's one-step bromomethylenation of diarylketones **1** was employed to create diarylvinyl bromides **3** by the combination of $CHBr_3$–$TiCl_4$–Mg in the co-solvent of DME and CH_2Cl_2.[10] Using the facile synthetic protocol, **3a–g** were isolated in acceptable 32–60% yields (Table 1, entries 1–6). Although the presented yields of **3** were unsatisfactory, it still was an efficient and straightforward route for synthesizing the skeleton of diarylvinyl bromides.

First, when a CuI-mediated cross-coupling reaction of phenol (**2a**) was treated with **3a** in toluene at 110 °C for 12 h in the absence of ligands, phenyl diphenylvinyl ether (**4a**) was afforded in only a 30% yield. In an attempt to improve the yield, four bidendate-based ligands (*N*,*N*-dimethylglycine (**L1**), 1,10-phenantholine (**L2**), 2,2′-bipyridine (**L3**), 2-pyridin-2-yl-1*H*-benzoimidazole (**L4**)) were examined.[6a–e] By testing the literature methodologies (Cs_2CO_3/1,4-dioxane, K_3PO_4/1,4-dioxane, Cs_2CO_3/toluene, K_3PO_4/toluene), **4a** was isolated in a range of 42–74% yields, as shown in

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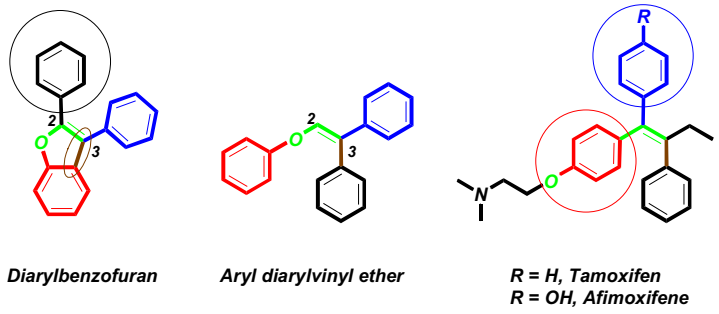
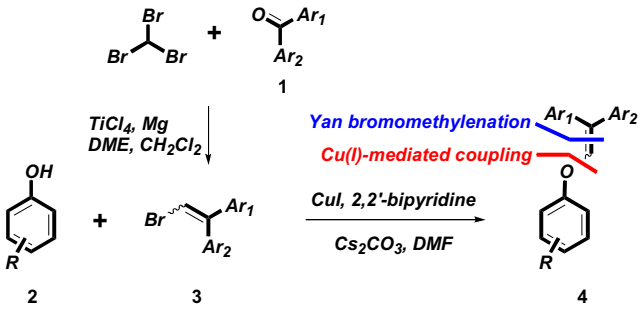
0040-4039/

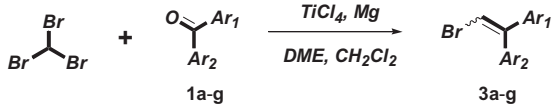


Scheme 1. Representative structures.



Scheme 2. Synthetic route toward skeleton **4**.

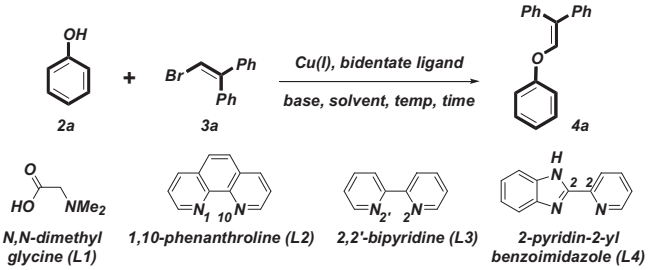
Table 1
Synthesis of **3a–g**[a]



Entry	**1**, Ar_1, Ar_2=	**3**, yield (%)[b]
1	**1a**, Ph, Ph	**3a**, 60
2	**1b**, Ph, 4-FPh	**3b**, 42 (1:2)[c]
3	**1c**, Ph, 4-MeOPh	**3c**, 57 (1:2)[c]
4	**1d**, 4-MeOPh, 4-MeOPh	**3d**, 51
5	**1e**, 4-MeOPh, 4-FPh	**3e**, 54 (1:1)[c]
6	**1f**, 4-FPh, 4-FPh	**3f**, 40
7	**1g**, 2-thiophene, Ph	**3g**, 32 (1:1)[c]

[a] The reaction was run on a 1.0 mmol scale with **1**, Mg (243 mg, 10.0 mmol), $TiCl_4$ (1.0 M in CH_2Cl_2, 1.0 mL, 1.0 mmol), $CHBr_3$ (0.3 mL), in the co-solvent of DME (1.5 mL) and CH_2Cl_2 (1.0 mL), ice bath to rt.
[b] Isolated yield.
[c] The ratio of *E*/*Z*-isomers was confirmed on the basis of ^1H or ^{13}C NMR analysis.

Table 2
Reaction condition of **4a**[a]



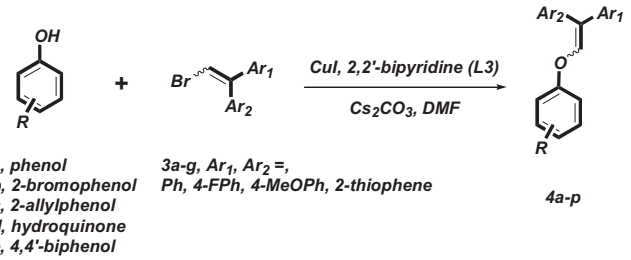
Entry	Ligand, base, solvent, temp (°C), time (h)	Yield (%)[b]
1	**L1**, Cs_2CO_3, 1,4-dioxane, 80, 24	52
2	**L2**, Cs_2CO_3, 1,4-dioxane, 80, 24	55
3	**L3**, Cs_2CO_3, 1,4-dioxane, 80, 24	75
4	**L4**, Cs_2CO_3, 1,4-dioxane, 80, 24	70
5	**L1**, K_3PO_4, 1,4-dioxane, 80, 24	42
6	**L2**, K_3PO_4, 1,4-dioxane, 80, 24	62
7	**L3**, K_3PO_4, 1,4-dioxane, 80, 24	70
8	**L4**, K_3PO_4, 1,4-dioxane, 80, 24	66
9	**L1**, Cs_2CO_3, toluene, 110, 24	50
10	**L2**, Cs_2CO_3, toluene, 110, 24	67
11	**L3**, Cs_2CO_3, toluene, 110, 24	78
12	**L4**, Cs_2CO_3, toluene, 110, 24	62
13	**L1**, K_3PO_4, toluene, 110, 48	54
14	**L2**, K_3PO_4, toluene, 110, 48	66
15	**L3**, K_3PO_4, toluene, 110, 48	74
16	**L4**, K_3PO_4, toluene, 110, 48	62
17	**L1**, Cs_2CO_3, DMF, 80, 24	66
18	**L2**, Cs_2CO_3, DMF, 80, 24	80
19	**L3**, Cs_2CO_3, DMF, 80, 24	88
20	**L4**, Cs_2CO_3, DMF, 80, 24	71

[a] The reaction was run on a 1.0 mmol scale with **2a**, **3a** (1.2 mmol), CuI (0.1 mmol), ligands (0.2 mmol), Cs_2CO_3 (1.2 mmol), solvent (2 mL).
[b] Isolated yield.

Table 2 (entries 1–4, 52–70%; entries 5–8, 42–70%; entries 9–12, 50–70%; entries 13–16, 54–74%). These experimental results showed that 2,2′-bipyridine (**L3**) provided a better yield. Furthermore, controlling the base (Cs_2CO_3), temperature (80 °C), solvent (DMF, 2 mL), and time (24 h) and switching four ligands **L1**–**L4**, we found that **4a** provided a better yield (88%). We thought that entry 19 was an optimal condition to increase the yield of **4a**. With this idea in mind, various substituted phenols were examined. The starting materials, substituted phenols **2** (phenol (**2a**), 2-bromophenol (**2b**), 2-allylphenol (**2c**), hydroquinone (**2d**) and 4,4′-biphenol (**2e**)) were easily afforded from commercially available materials. By the abovementioned protocol, products **4a–p** were isolated in DMF at 80 °C for 24 h via the CuI-mediated cross-coupling of **2a–e** and **3a–g** with the combination of Cs_2CO_3 and 2,2′-bipyridine (**L3**).

As shown in Table 3, **4a–p** with electron-donating, electron-neutral, or electron-withdrawing substituents (Ar_1, Ar_2 = Ph, 4-FPh, 4-MeOPh, 2-thiophene) were produced in a range of moderate yields (70–88%). No obvious yield changes in all the entries were exhibited besides **4a**, **4b**, and **4c** which provided better (88%, 82%, and 83%) yields, respectively, (by the classical CuI-mediated cross-coupling of **2a** with **3a–b** and **3g**). The experimental results showed that the cross-coupling reaction of **2b** bearing a 2-bromo substituent with **3a–c** provided 74–78% yields of **4d–f**, and no expected skeleton of dibenzo[1,4]dioxine was observed (by the self-coupling of **2b**). Similar results were described in the formation of **4g–j** from the cross-coupling reaction of 2-allylphenol (**2c**) with **3a–b** and **3d–e**. Furthermore, the double cross-coupling reactions of **2d** or **2e** with **3a–c** or **3a** and **3f** performed well. A selective mono-cross coupling reaction of **2e** with **3a** was also achieved to **4n** in a 73% yield. For the *E*/*Z*-isomers of **4b**, **4c**, **4e**,

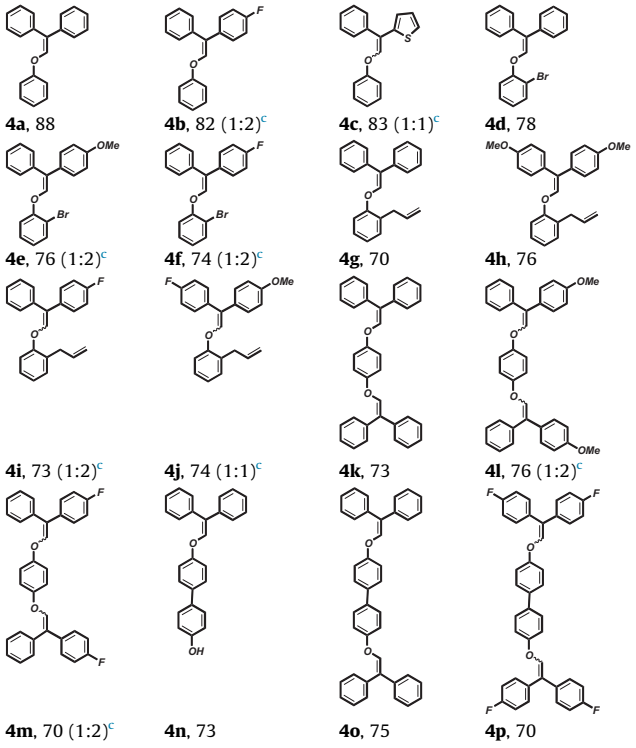
Table 3
Synthesis of **4a**–**p**[a-b]



2a, phenol
2b, 2-bromophenol
2c, 2-allylphenol
2d, hydroquinone
2e, 4,4′-biphenol

3a-g, Ar_1, Ar_2 =,
Ph, 4-FPh, 4-MeOPh, 2-thiophene

4a-p



4a, 88 | **4b**, 82 (1:2)[c] | **4c**, 83 (1:1)[c] | **4d**, 78

4e, 76 (1:2)[c] | **4f**, 74 (1:2)[c] | **4g**, 70 | **4h**, 76

4i, 73 (1:2)[c] | **4j**, 74 (1:1)[c] | **4k**, 73 | **4l**, 76 (1:2)[c]

4m, 70 (1:2)[c] | **4n**, 73 | **4o**, 75 | **4p**, 70

[a] The reaction was run on a 1.0 mmol scale with **2a**–**e**, **3a**–**g** (1.2 or 2.4 mmol), CuI (0.1 or 0.2 mmol), **L3** (0.2 or 0.4 mmol), Cs_2CO_3 (1.2 or 2.4 mmol), DMF (2 mL).
[b] Isolated yields.
[c] The ratio of *E*/*Z*-isomers was confirmed on the basis of ^1H or ^{13}C NMR analysis.

4f, **4i**, **4j**, **4l**, and **4m**, related ratios were confirmed on the basis of ^1H or ^{13}C NMR analysis. The structural framework of **4k** was determined by single-crystal X-ray crystallography.[11] The representative ORTEP of **4k** proved the constitution and relative configuration, as shown in Figure 1.

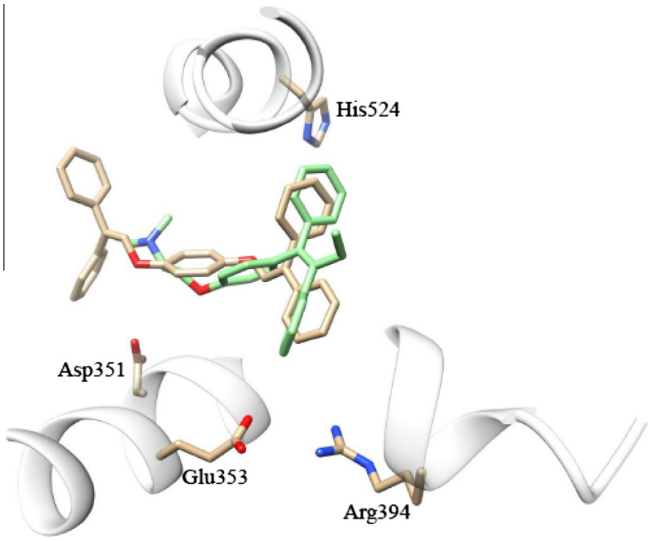


Figure 2. Our docking experiments show that **4k** (golden) can be a stronger binder to estrogen receptor (ER) than Tamoxifen (green). Of best docked poses, both **4k**'s hydroquinone moiety and Tamoxifen's trimethylamine have the inhibitory hydrogen bonding to the ER Asp351 while **4k** has an extended diphenyl group deep into the ER binding pocket.

Further CADD (computer assisted drug design) docking experiments indicated that **4k** (with the docking score, 66.6) can be a stronger binder to estrogen receptor (ER) than Tamoxifen (55.8). As shown in Figure 2, the docked poses revealed that **4k** bears a hydroquinone moiety yielding the inhibitory hydrogen bonding to the residue Asp351, similar to the role of Tamoxifen's trimethylamine in the ER binding pocket. We believe that a further diphenyl group extended into the binding pocket can make **4k** a good antagonist in respect to the machinery of ER antagonism.[12]

Conclusion

In summary, we have successfully presented an efficient and straightforward synthetic route for the synthesis of substituted aryl diarylvinyl ethers **4** via a CuI-mediated cross-coupling reaction of substituted phenols **2** with diarylvinyl bromides **3** in the presence of 2,2′-bipyridine ligand in DMF. The synthetic route obtained

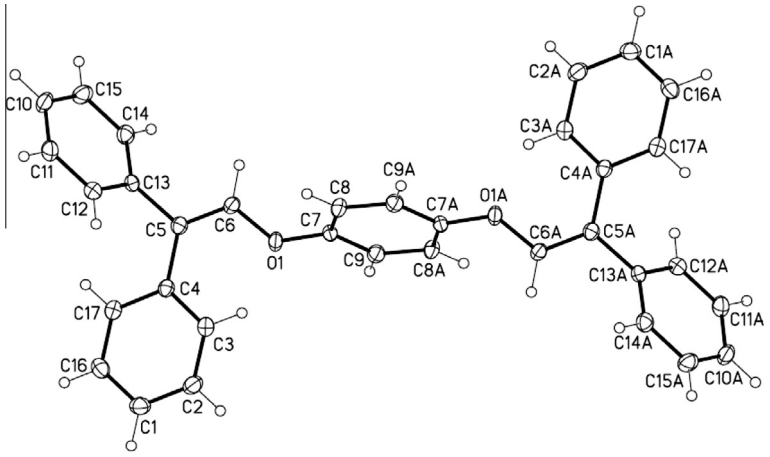


Figure 1. X-ray structure of **4k**.

moderate yields. Further investigation regarding CuI mediating the intramolecular structure of phenol analogs with aryl halides will be conducted and published in due course.

Acknowledgments

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Supplementary data

Supplementary data (Scanned photocopies of ^{1}H and ^{13}C NMR spectral data as well as details of the docking experiments.) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.10.018.

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