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Selenium-Mediated Synthesis of Biaryls through Rearrangement

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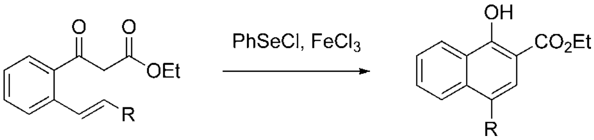
ABSTRACT



A new cyclization of β-keto ester substituted stilbene derivatives using selenium electrophiles in the presence of Lewis acids is described. Substituted naphthols are obtained through cyclization and subsequent 1,2-rearrangement of aryl groups under very mild reaction conditions.

Selenium reagents have a very broad spectrum of applications and are used as key reagents in organic synthesis.[1] Usually mild reaction conditions and high selectivities are associated with selenium reagents. The formation of new carbon−carbon bonds through electrophilic addition to double bonds is an attractive strategy in organic synthesis. However, carbocyclizations mediated by selenium electrophiles have not been investigated in much detail.[2,3]

Polysubstituted naphthalenes are being used in many areas such as pharmaceuticals, plant protection agents, dyes, and many others.[4] In addition, some natural products with naphthalene or biaryl structures often exhibit biological activities such as antimalarial properties and potent anti-HIV activity or show potential for the treatment of diabetes and cancer.[5] Apart from their interesting biological activity, biarylnaphthalene compounds also find application as chiral reagents, ligands, and metal complexes in synthesis.[6]

Recently, we have reported the synthesis of dihydronaphthalene and benzofluorene derivatives by selenium-mediated cyclizations of malonate moieties onto alkenes.[7] Herein we use a similar approach for the synthesis of the stilbene starting materials based on Mizoroki−Heck reactions, hydrolysis, and condensation steps. The palladium-catalyzed cross-coupling reaction of methyl 2-iodobenzoate **1** with different styrene derivatives afforded esters **2** in good yields, and subsequent hydrolysis yielded the corresponding carboxylic acids **3** almost quantitatively (Scheme 1). Condensation of the carboxylic acid with potassium ethyl malonate in the presence of triethylamine and magnesium dichloride afforded the β-keto ester derivatives **4**. NMR investigations revealed that the stilbene β-keto esters **4** are in equilibrium

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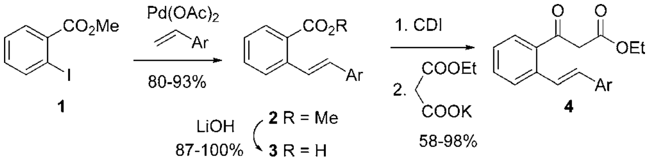
10.1021/ol100274e

with their corresponding enol forms with the equilibrium largely shifted toward the keto form.

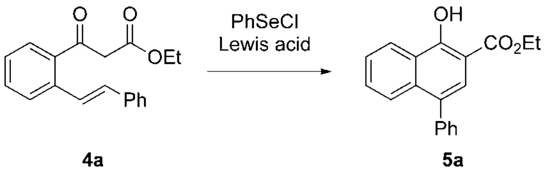
Scheme 1. Synthesis of the Cyclization Precursors **4**



As part of our ongoing research in the cyclofunctionalization of stilbenes for the construction of carbocycles, we recently reported a cascade biscarbocyclization using a reagent combination of selenium electrophiles and Lewis acids.[7] The same reagent combination is now used for the cyclization of β-keto esters **4**. The treatment of β-keto ester **4a** with phenyl selenenyl chloride and titanium tetrachloride resulted only in the 6-*endo* cyclization product **5a**: the corresponding 5-*exo* cyclization product was not observed. The selenium moiety was eliminated under the reaction conditions as we have already observed in other examples,[7] and the naphthol derivative **5a** was isolated in 61% yield. Careful analysis of the product **5a** also revealed that a migration of the phenyl group had taken place as this is now found in the 4-position. Spectroscopic data of **5a** are in agreement with literature values,[8] but final proof of the structure was an X-ray analysis obtained from crystals of compound **5a**.[9] Other Lewis acids and reaction conditions were screened which resulted in different yields of **5a**; some of these results are shown in Table 1.

The Lewis acids $FeCl_3$ and $ZrCl_4$ provided the highest yield in this reaction with short reaction times under very mild conditions (Table 1, entries 6 and 9). Optimization experiments revealed that the optimal combination is $FeCl_3$ with PhSeCl as very good yield are obtained in only 30 min reaction time (entry 6). When $BF_3 \cdot OMe_2$ (2.5 equiv) was used in the presence of PhSeCl, the product was obtained within 4 h in 75% yield (entry 4). The combination of phenyl selenenyl chloride with many Lewis acids are more and less effective for this C−C bond formation, and the corresponding substituted naphthalene **5a** was obtained after rearrangement of the aryl substituent. Less reactive Lewis acids such as $BF_3 \cdot OMe_2$ can be used at room temperature. To test the feasibility of this carbocyclization without PhSeCl, stilbene **4a** was reacted with either $BF_3 \cdot OMe_2$ (2.5 equiv) or $ZrCl_4$ (2.5 equiv), but even after prolonged time (2 days) no reaction was observed (Table 1, entries 7 and 11). However, when only iron(III) chloride (2.5 equiv) was used for the cyclization, the yield dropped to 40% (Table 1, entry 8). In addition, it was found that 1.1 equiv of the Lewis acid are sufficient (Table 1, entries 5 and 6).

Table 1. Cyclization of **4a** to Naphthol **5a**



entry	Lewis acid (equiv)	PhSeCl (equiv)	reaction time (h)	temp (°C)	yield of **5a** (%)
1	$TiCl_4$ (2.5)	1.5	10	−78	61
2	$SnCl_4$ (2.5)	1.5	10	−78	59
3	$AlCl_3$ (2.5)	1.5	1	−78	70
4	$BF_3 \cdot OMe_2$ (2.5)	1.5	4	20	75
5	$FeCl_3$ (2.5)	1.8	0.5	−78	79
6	$FeCl_3$ (1.1)	2.0	0.5	−78	82
7	$BF_3 \cdot OMe_2$ (2.5)		48	20	traces
8	$FeCl_3$ (2.5)		50	20	40
9	$ZrCl_4$ (1.1)	2.0	2	−78	80
10	$ZrCl_4$ (1.1)	1.0	2	−78	45 (conversion)
11	$ZrCl_4$ (2.5)		48	−78	no reaction

With these optimized reaction conditions, the scope and limitation of this reaction were examined. The results in Table 2 demonstrate that the reaction proceeds smoothly with various substituted stilbenes to afford 4-substituted naphthalen-1-ols in good yields (entries 1−7, Table 2).

With aromatic substituents R, the substrates **4** underwent facile cyclization and migration of the aryl moiety R to the neighboring sp^2-hybridized carbon atom. It is necessary to maintain the temperature at −78 °C to obtain good yields. Binaphth-4-ols **5b** and **5c** were obtained in 81 and 83% yield, respectively. This reaction could also serve as an entry into the synthesis of various substituted binaphthyl derivatives (Table 2, entries 1 and 2). Treatment of other aryl-substituted substrates **4** with phenylselenenyl chloride in the presence of iron(III) chloride underwent 6-*endo* cyclization to the corresponding products **5d−h** in very good yields (Table 2, entries 3−7).

These results are particularly significant when considering that there are more complicated routes to synthesize 4-aryl-substituted naphthalen-1-ol derivatives.[10] Related benzannulation reactions have also been described.[11] Electron-poor aryl groups afford slightly lower yields, but electron-rich moieties (Table 2, entry 7) gave facile migration of the aryl group to produce aryl-substituted naphthalen-1-ols in high yield. The methyl-substituted starting material **4i** (R = Me) was prepared using a Wittig reaction to synthesize methyl 2-(prop-1-en-1-yl)benzoate **2i** (R = Ar = Me). In the

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(8) Taylor, G. A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 3132.

(9) CCDC-760701 (**5a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or e-mail: deposit@ccdc.cam.ac.uk).

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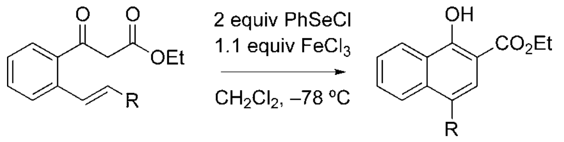
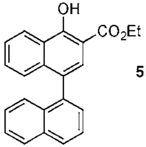
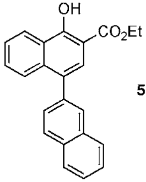
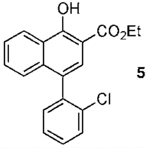
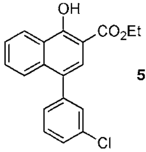
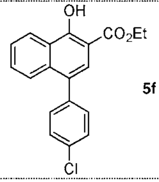
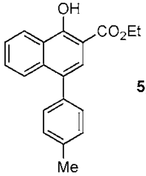
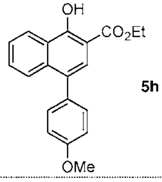
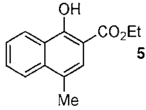
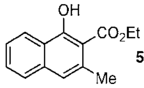
(11) (a) Ciufolini, M. A.; Weiss, T. J. *Tetrahedron Lett.* **1994**, *35*, 1127. (b) Belmont, P.; Andrez, J. C.; Allan, C. S. M. *Tetrahedron Lett.* **2004**, *45*, 2783. (c) Belmont, P.; Parker, E. *Eur. J. Org. Chem.* **2009**, 6075.

Table 2. Cyclization of **4** to Rearranged Naphthols **5**



4 **5**

entry	R	product	reaction time [h]	yield **5** [%]
1	1-naphthyl	 **5b**	3	81
2	2-naphthyl	 **5c**	3	83
3	2-Cl-C_6H_4	 **5d**	1.5	81
4	3-Cl-C_6H_4	 **5e**	1.5	68
5	4-Cl-C_6H_4	 **5f**	5	69
6	4-Me-C_6H_4	 **5g**	1	80
7	4-OMe-C_6H_4	 **5h**	1	96
8	4-OMe-C_6H_4	**5h**	10	70[a]
9	Me	 **5i**  **5j**	2.5	50

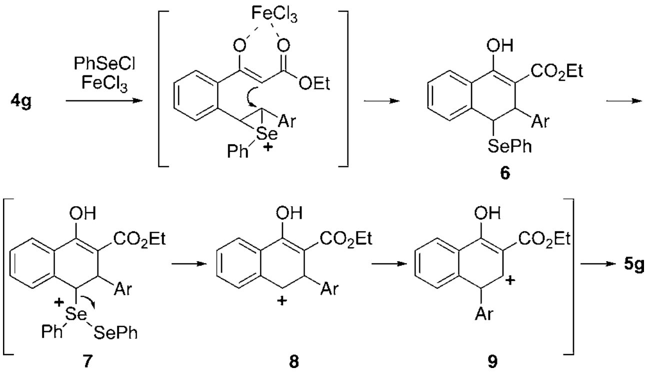
[a] 1.1 equiv of $(PhSe)_2$ and 1.4 equiv of $PhI(OCOCF_3)_2$ used as reagents.

cyclization of alkene **4i** a decrease in yield as well as the formation of two cyclization products was observed. Naphthalen-1-ol **5i** and **5j** were obtained in a 2:1 ratio and 50% combined yield (Table 2, entry 9). Together with the rearranged product **5i**, compound **5j** without rearrangement of the methyl group was formed. Separation of the two isomers was not possible.

We have already shown that bis(trifluoroacetoxy)iodobenzene and catalytic amounts of diphenyl diselenide is an effective reagent combination for the synthesis of butenolides.[12] For the carbocyclization of **5h**, however, only the combination of bis(trifluoroacetoxy)iodobenzene with stoichiometric amounts of diphenyl diselenide led to product formation via the phenylselenenyl trifluoracetate as reactive selenium electrophile (Table 2, entry 8). When the hypervalent iodine reagent is used as the single electrophile without diphenyl diselenide, only small amounts of the product **5h** are formed together with side products.

For an investigation of the reaction mechanism, it was decided to stop a reaction after 15 min. The key intermediate, the phenylseleno-substituted 3,4-dihydronaphthalene **6**, was isolated by preparative TLC. The subsequent activation of the selenide by a second selenium electrophile (**7**) produces the carbocationic intermediate **8**, which then rearranges to **9** and, after rearomatization, generates **5g** as single reaction product (Scheme 2).

Scheme 2. Proposed Mechanism for the Synthesis of Compounds **5** through Rearrangement[a]



[a] Ar = 4-Me-C_6H_4.

The carbocations **8** and **9** with Ar = Ph (from **4a**) and Ar = Me (from **4i**) were calculated as methyl esters instead of ethyl esters. The ab initio calculations were performed using the Gaussian 03 program.[13] Geometries were fully optimized at B3LYP/6-31G(d) level using the pcm solvent model for dichloromethane, and the obtained energy minimum structures were characterized by frequency calculation at the same calculation level. It was found that both cations **9** (Ar = Ph and Ar = Me) are more stable than the cations **8** by approximately 14.5 kcal/mol. Attempts to locate a phenonium

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(12) Browne, D. M.; Niyomura, O.; Wirth, T. *Org. Lett.* **2007**, *9*, 3169.

ion intermediate as observed by us in other cyclizations[14] failed. Details are included in the Supporting Information.

In conclusion, we present a new cyclization of stilbene derivatives with a β-keto ester functionality using selenium electrophiles in the presence of Lewis acids. The resulting substituted naphth-1-ols are obtained through cyclization and subsequent 1,2-rearrangement of aryl and alkyl groups under very mild reaction conditions.

It is envisioned that this reaction will find applications in the synthesis of natural products, and this methodology will serve as a fast and convenient access to interesting naphthalene and biaryl compounds.

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Supporting Information Available: Experimental procedures for the synthesis of compounds **2−6** and spectral data for new compounds as well as computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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