Benzofluorenes

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Fast Synthesis of Benzofluorenes by Selenium-Mediated Carbocyclizations**

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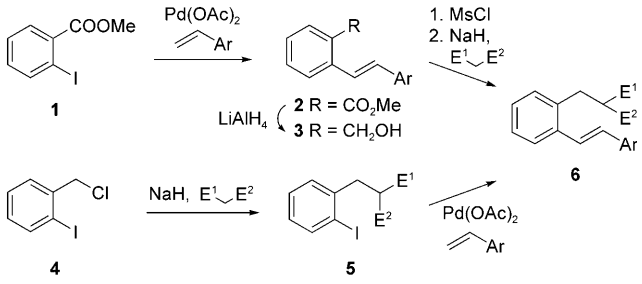
The formation of new carbon–carbon bonds through electrophilic addition to double bonds is a highly attractive method in organic synthesis, because the products can be achieved directly from readily available starting materials without forming copious amounts of by-products. However, carbocyclizations mediated by selenium electrophiles have not been investigated in much detail.[1] Early examples include selenium-promoted carbocyclizations using dicarbonyl compounds as nucleophiles together with Lewis acids such as zinc iodide, tin tetrachloride, and aluminium trichloride, under strong acidic conditions.[2] The electrophilic cyclization of substituted propargylic aryl ethers by phenyl selenenyl bromide produces 3,4-disubstituted 2*H*-benzopyrans in excellent yields.[3] Spirocompounds can also be synthesized by a titanium tetrachloride promoted transfer of a phenylseleno moiety in α-phenylseleno alkenyl ketones.[4] More recently, asymmetric versions of the selenium-mediated carbocyclizations have been reported.[5]

In the synthesis of the tetracyclic core of benzo[*b*]fluorenes, which are prominently featured in some natural compounds exhibiting interesting biological activity, we prepared different dihydronaphthalenes as their immediate precursors. In recent years, synthetic efforts in this area have resulted in the synthesis of natural[6] and non-natural benzo[*b*]fluorenes.[7] Some of these derivatives have been used in the study of cationic intermediates[8] or were found to be promising compounds for the construction of organic light-emitting diodes.[9] Intramolecular [4+2] cycloadditions of 2-propynyl diarylacetylenes[10] or radical cycloaromatizations of non-conjugated benzotriynes[11] can lead to benzo[*b*]fluorene derivatives; additionally, palladium-mediated arylations to benzo[*b*]fluorenes have been investigated.[12] The rapid construction of benzo[*b*]fluorenones through the reaction of 1-indanone dianions with phthalate diesters was achieved, resulting in a concise synthesis of prekinamycin.[13] The thermal cyclizations of diaryl diynones led to benzo[*b*]fluorenes by a rearrangement process.[14]

Most of these classical methods for the preparation of benzo[*b*]fluorenes have some drawbacks, such as long reaction sequences, use of expensive reagents, or high temperatures. To the best of our knowledge, there has been no report on the tandem double cyclization reaction involving a carbon–carbon double bond activation by using phenyl selenenyl chloride as the electrophile. Herein, we report a novel, selenium-mediated tandem double cyclization reaction consisting of a sequence of carboannulation and Friedel–Crafts acylation, and a subsequent rearrangement process. This sequence has been proven to be a useful tool in the synthesis of dihydronaphthalenes and benzofluorenes from easily accessible stilbenes, and provides fast access to polycyclic ring systems in a single step.

The synthesis of stilbene compounds derived from methyl 2-iodobenzoate (**1**) involved a sequence of palladium-catalyzed Heck reactions to give the stilbenes **2**, reduction to give **3**, mesylation, and subsequent nucleophilic substitution to produce compounds **6** in a very good overall yield. Alternatively, 2-iodobenzyl chloride (**4**) served as the starting material in a similar route through **5** to target substrates **6** (Scheme 1).



Scheme 1. Synthesis of stilbene derivatives **6**.

Initial experiments were carried out using the phenyl-substituted derivative **6a** (Scheme 2). The deprotonation of stilbene **6a** with sodium hydride and reaction with phenylselenenyl chloride led to the formation of **7a** in 49% yield. Unfortunately, compound **7a** decomposed to starting material **6a** upon standing at room temperature. Therefore, the subsequent Lewis acid mediated cyclization was performed directly by treatment with either tin tetrachloride or titanium tetrachloride leading to dihydronaphthalene **8a** in 35% or 37% yield, respectively (Table 1, entries 1 and 2). The cleavage of the selenium–carbon bond mediated by the Lewis acid could lead to the formation of a selenium

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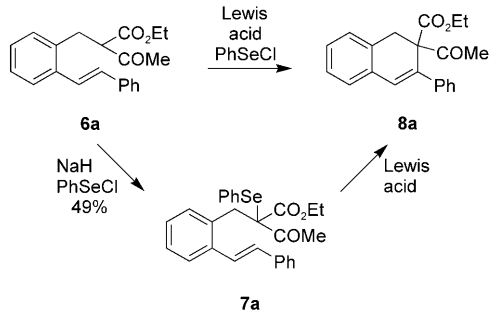


Scheme 2. Selenium-mediated carbocyclization of stilbene derivative **6a** to dihydronaphthalene **8a**.

Table 1: Optimization of the reaction conditions for the selenium-mediated carbocyclization to **8a**.

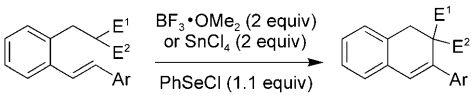
Entry	Substrate	Reagents[a]	*t* [h]	Yield of **8a** [%]
1	**7a**	$TiCl_4$ (1.5 equiv)	16	37
2	**7a**	$SnCl_4$ (2 equiv)	16	35
3	**6a**	$SnCl_4$ (2 equiv)	144	0
4	**6a**	$TiCl_4$ (2 equiv), PhSeCl (1.1 equiv)	16	86
5	**6a**	$SnCl_4$ (2 equiv), PhSeCl (1.1 equiv)	16	77
6	**6a**	$BF_3{\cdot}OMe_2$ (2 equiv), PhSeCl (1.1 equiv)	22	90

[a] Reaction conditions: −60 °C→RT.

electrophile, which would subsequently activate the double bond for the carbocyclization. As the overall yields are quite low, we evaluated the scope of a one-pot cyclization/elimination sequence by combining a Lewis acid with the selenenylating reagent as shown in Table 1. The cyclization does not occur in the absence of the selenium electrophile (Table 1, entry 3). The combination of boron trifluoride dimethyl etherate and phenylselenenyl chloride (Table 1, entry 6) was found to be the optimal reaction conditions leading to the expected dihydronaphthalene compound **8a** in 90% yield. The structure of **8a** was additionally confirmed by X-ray crystallographic analysis.[15] Various other substrates of type **6** have been cyclized in such a selenium-mediated reaction and dihydronaphthalene derivatives **8** have been obtained as shown in Table 2.

When exposed to boron trifluoride dimethyl etherate for a longer time, we observed that dihydronaphthalene **8a** was undergoing a subsequent Friedel–Crafts-type cyclization through a novel rearrangement. Upon the addition of boron

Table 2: Selenium-mediated carbocyclization of stilbenes **6** to dihydronaphthalenes **8**.



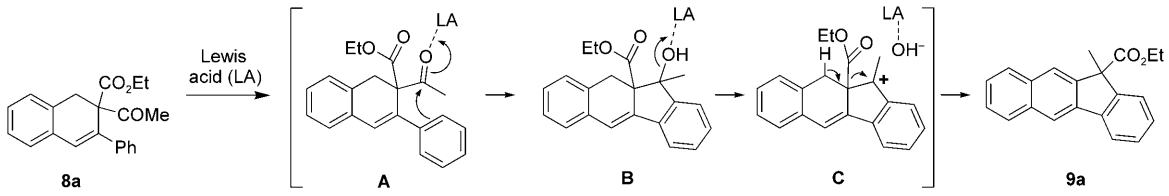
6 **8**

Entry	Substrate	Ar	E^1	E^2	*t* [h]	Yield of **8** [%]
1	**6a**	Ph	CO_2Et	COMe	22	90[a]
2	**6b**	2-ClC_6H_4	CO_2Et	COMe	16	74[b]
3	**6c**	3-ClC_6H_4	CO_2Et	COMe	16	68[b]
4	**6d**	4-ClC_6H_4	CO_2Et	COMe	22	78[a]
5	**6e**	2,6-$Cl_2C_6H_3$	CO_2Et	COMe	16	82[b]
6	**6f**	Ph	CO_2Me	CO_2Me	36	50[b]

[a] Reaction conditions: $BF_3{\cdot}OMe_2$ (2 equiv), −60 °C, 15 min, then PhSeCl, −60 °C→RT. [b] Reaction conditions: $SnCl_4$ (2 equiv), −60 °C, 15 min, then PhSeCl, −60 °C→RT.

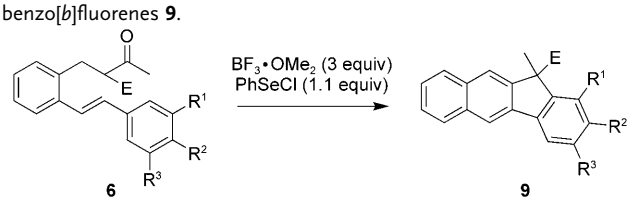
trifluoride dimethyl etherate at −60 °C and subsequent addition of phenyl selenenyl chloride, compound **6a** was converted into dihydronaphthalene **8a**, as observed by ^{1}H NMR analysis of the crude reaction mixture after 12 hours of stirring at room temperature. If the compound **8a** is exposed for a longer time (3 days) to boron trifluoride dimethyl etherate at room temperature, the rearrangement to a tetracyclic compound occurred and was isolated in good yields (Scheme 3). The reaction time is critical for obtaining the products from a double carbocyclization process. For an additional investigation into the mechanism of the tandem double cyclization reaction, dihydronaphthalene **8a** was treated with boron trifluoride dimethyl etherate and led to the tetracyclic product in quantitative yield. With dihydronaphthalene **8f**, however, the same reaction protocol failed to afford the tetracyclic product even after a reaction time of one week. It seems that the subsequent reaction cascade is sensitive to the electronic properties of the molecule; dihydronaphthalenes **8b–8d** also did not form any tetracyclic products. However, this reaction could be extended to other electron-rich stilbene derivatives. The treatment of compounds **6g–6k** with boron trifluoride dimethyl etherate or other Lewis acids, and using phenyl selenenyl chloride as selenium electrophile allowed the straightforward synthesis of benzo[*b*]fluorenes **9** in good yields as shown in Table 3.

The formation of the tetracyclic compounds **9** shows that this tandem reaction involves a novel rearrangement process by activation of the double bond, which results in a total of three C–C bond formations, and a C–C and C–O bond cleavage, leading to the formation of tetracyclic compounds **9**.



Scheme 3. Mechanistic proposal for the Friedel–Crafts cyclization and subsequent ester rearrangement of dihydronaphthalene **8a** to benzo[*b*]-fluorene **9a**.

Table 3: Selenium-mediated double carbocyclization of stilbenes **6** to benzo[*b*]fluorenes **9**.



6 **9**

Entry	Substrate	R^1	R^2	R^3	E	*t* [h]	Yield of **9** [%]
1	**6a**	H	H	H	CO_2Et	72	90
2	**6a**	H	H	H	CO_2Et	70	30[a]
3	**6g**	H	Me	H	CO_2Et	60	80, 87[b]
4	**6h**	H	OMe	H	CO_2Et	69	67
5	**6i**	H	H	Me	CO_2Et	72	67[c]
6	**6j**	CH=CH–CH=CH		H	CO_2Et	50	82[d]
7	**6k**	H	H	H	COMe	27	85[e]

[a] Conversion given, only 0.3 equivalents of $BF_3{\cdot}OMe_2$ used. [b] 2 equivalents of $SnCl_4$ used instead of $BF_3{\cdot}OMe_2$ as the Lewis acid. [c] Product **9i** obtained as a 1:1 mixture of regioisomers ($R^1=R^2=H$, $R^3=Me$ and $R^2=R^3=H$, $R^1=Me$). [d] Product **9j** obtained as only one regioisomer. [e] 2 equivalents of $TiCl_4$ used instead of $BF_3{\cdot}OMe_2$ as the Lewis acid.

The structure of **9j** was additionally confirmed by X-ray crystallographic analysis.[15]

We also observed the formation of benzo[*b*]fluorene **9h** in low yields when other Lewis acids ($TiCl_4$, $SnCl_4$) were used at room temperature instead of low reaction temperatures. The presence of electron-donating substituents R on the aromatic moiety of **6** seems to be crucial for the success of the double cyclization process. If only substoichiometric amounts of the Lewis acid is used (Table 3, entry 2), the conversion drops significantly; with 0.3 equivalents of boron trifluoride dimethyl etherate only 30% conversion are observed. Longer reaction times do not improve the conversion. Stoichiometric amounts of the Lewis acid are therefore required in this reaction.

We propose the generation of an intermediate carbocation by reaction with the Lewis acid (**C**) as the step after the intramolecular Friedel–Crafts acylation from **A** to **B**. The aromatization of **C** leads to a 1,2-migration of the ester moiety and formation of benzo[*b*]fluorene derivative **9a** as the thermodynamically most stable product. Similar 1,2-migrations of ester moieties under the assistance of Lewis acids have been reported in literature.[16] The generation of equimolar amounts of water in this cyclization leads to a complexation/inactivation of the Lewis acid, therefore stoichiometric amounts are required. Interestingly, substrate **6k** (Table 3, entry 7), containing two methylketone moieties, showed that a migration of a methylketone substituent is possible under the reaction conditions and the product **9k** was isolated in 85% yield.

In conclusion, we have developed a tandem double cyclization of stilbenes with a selenium electrophile and a Lewis acid, which afforded various novel benzofluorenes in a one-pot reaction from simple starting materials. This work represents the first example of an intramolecular carbon–carbon bond formation promoted by selenium electrophiles to dihydronaphthalenes which are additionally transformed to benzofluorenes through a unprecedented Lewis acid mediated double cyclization reaction involving a new rearrangement process.

Experimental Section

Typical procedure: $BF_3{\cdot}OMe_2$ (1.5 mmol, 0.138 mL) was added to a solution of **6a** (0.5 mmol, 161 mg) in dichloromethane (4 mL) at room temperature. After stirring for 15 min, phenyl selenenyl chloride (0.55 mmol, 105 mg) was added in one portion and the reaction mixture was then stirred for 60 h at room temperature. The mixture was quenched by the addition of H_2O (10 mL) and then extracted with diethylether (3×10 mL). The combined organic extracts were dried with $MgSO_4$, filtered, evaporated under reduced pressure, and the crude product was then purified using silica gel chromatography and ethyl acetate/hexanes (1:12) as an eluent to give the title compound **9a** as a light yellow viscous oil in 90% yield (0.45 mmol, 136 mg).

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