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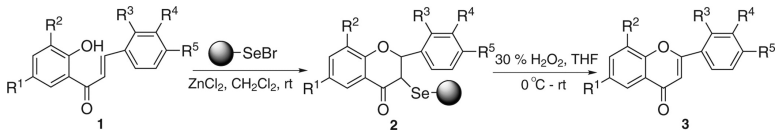

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Lewis Acid Catalyzed Solid-Phase Synthesis of Flavonoids Using Selenium-Bound Resin

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Introduction. Combinatorial chemistry is becoming an increasingly important tool in both chemical biology and drug discovery.[1] The development of more efficient strategies for the construction of libraries of natural-like or druglike compounds is important for chemists to study cellular functions and to search for novel drug candidates.[2]

In the course of our ongoing efforts directed toward the solid-phase synthesis,[3] we were interested in the combinatorial diversification of flavonoids. Flavonoids are natural products from plants,[4] which have been shown to elicit antitumoral, antiplatelet, antiischemic, antiallergic, and anti-inflammatory activities.[5] Many syntheses of flavonoids have already been reported.[6] Among them, methods reported by Baker-Venkataraman,[6o−6p] Allan-Robinson,[6q] and Algar-Flynn-Oyamada[6r−6s] are the most widely employed; however, to the best of our knowledge, there have not been any solid-phase syntheses of flavonoids.

Since the first synthesis in 1976, organoselenium resins[7] have been successfully used as convenient linkers for the synthesis of indolines, benzopyrans, and ortho esters, etc.[8] Recently, our research group has been interested in the application of organic selenium resins in organic synthesis.[3,9] We now report a simple solid-phase synthesis of flavonoids from the Lewis acid-mediated polystyrene-supported selenium-induced intramolecular cyclization of chalcones and the subsequent oxidative cleavage of selenium resins. Advantages of this method are easy operations, mild reaction conditions, odorlessness, good yields, and high purities of the products.

Results and Discussion. The solid-phase cyclization of 2-hydroxylchalcone **1a** with polystyrene-supported selenenyl bromide (dark-red resin; Br, 1.01 mmol/g) was explored under the conditions reported by Nicolaou.[8a,8b] But the selenium resin-bound product was not obtained, since the IR spectrum of the resulting resin did not show any absorption of the expected carbonyl group. The difficulty of the above selenium-induced cyclization may be reasoned by the electron deficiency of the double bond conjugated with the carbonyl group in **1a** (Table 1).

Fortunately, we observed that in the presence of 40 mol % $ZnCl_2$, the reaction of 5.0 equiv of **1a** with polystyrene-supported selenenyl bromide at room temperature for 12 h afforded the best result (Table 1, entry 7). The employment of 40 mol % $AlCl_3$ or $FeCl_3$ afforded the product in 18 or 24% yields, respectively. No product was obtained when other Lewis acids, such as $TiCl_4$, $BF_3{\cdot}Et_2O$, or $SnCl_4{\cdot}4H_2O$, was used (Table 1, entries 1−2 and 10). Prolongation of the reaction time did not improve the yield significantly (Table 1, entry 9).

It was observed that the decolorization of polystyrene-supported selenenyl bromide occurred when 3.0 equiv of the compound **1a** was used. After being stirred at room temperature for 12 h, the solid-phase ring-closure reaction was completed, and the elemental analysis of resin **2a** showed that no Br presented. The reaction was also monitored by FT-IR, which showed a strong peak of the carbonyl absorption at 1685 cm^{-1} in the resulting resin **2a**. As a result, the optimized conditions of the cyclization reaction were 3.0 equiv of **1a**, 40 mol % of $ZnCl_2$, and 1.0 g of polystyrene-supported selenenyl bromide in 20 mL of CH_2Cl_2 at room temperature for 12 h.

To test the scope of this SPOS protocol, the polystyrene-supported selenium-induced cyclization reactions of a series of substituted 2-hydroxylchalcones **1** were studied under the above conditions. The results are summarized in Table 2. HPLC analysis shows that the purities of the products are >90% in most cases.

So far, more than 4000 different flavonoids have been isolated from plants.[10] The diversity arises from the various hydroxylation, alkoxylation, and glycosylation patterns of the aromatic ring. The initial loading of various substitutent in chalcones **1** provided functionalized resin-bound flavonanes **2** for the further elaboration toward the skeletons of various flavone-containing natural products. We chose 2-hydroxyl-4′-hydroxylchalcone **1e** as the example for the further transformation to other flavonoids. In the presence of K_2CO_3 and KI, the resulting resin-bound 4′-hydroxylflavonane **2e** underwent alkylation[11] with primary or secondary alkyl bromide smoothly to give resin-bound 4′-alkoxylflavonanes **4**, which was followed by oxidative cleavage to provide 4′-alkoxylflavones **5** in total yields of 56−68%, respectively (Table 3, entries 1−5). Because of the elimination reaction of *t*-BuCl under basic conditions, we did not get any alkylated product when *t*-BuCl was used. Arylation reaction of resin **2e** did not occur; even activated aryl halide was used under the same conditions. Upon further investigation, we found that the starting material 2-hydroxyl-4′-hydroxylchalcone **1e** was obtained when KOH was used instead of K_2CO_3 during the efforts toward arylation. But this could be solved when diaryliodonium salts were used instead of aryl halide to perform the arylation reaction (Table 3, entries 6−7). The results are summarized in Table 3.

Due to their antioxidant properties,[5] biological activities, such as antiviral, anticoagulation, antibacterial, and modula-

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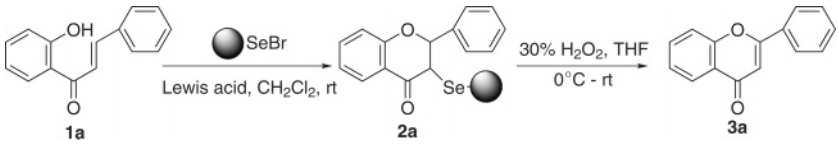
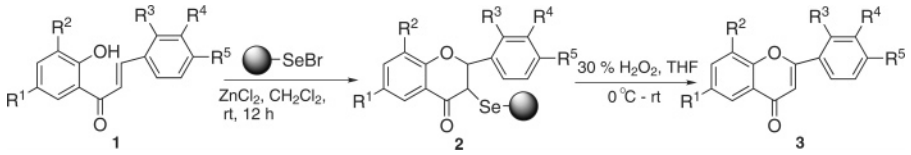
Table 1. Optimization of Solid-Phase Conditions of Cyclization



entry	Lewis acid	mol %	time h	yield of **3a**[a] %	purities[b] %
1	$TiCl_4$	40	12	nr	
2	$BF_3{\cdot}Et_2O$	40	12	nr	
3	$AlCl_3$	40	12	18	>80
4	$FeCl_3$	40	12	24	>80
5	$ZrCl_4$	40	12	12	>80
6	$ZnCl_2$	20	12	64	>95
7	$ZnCl_2$	40	12	82	>95
8	$ZnCl_2$	60	12	80	>95
9	$ZnCl_2$	40	24	83	>95
10	$SnCl_4{\cdot}4H_2O$	40	12	nr	

[a] Yields of the crude products based on the loading of selenium bromide resin (Br, 1.01 mmol/g). [b] Determined by HPLC analysis.

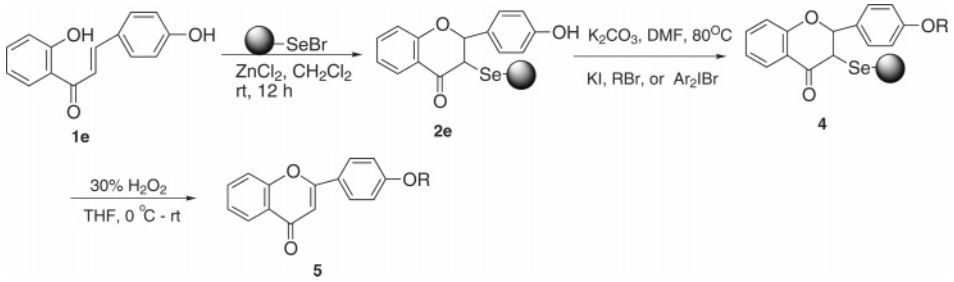
Table 2. Solid-Phase Synthesis of Flavonoids **3**



entry	R^1	R^2	R^3	R^4	R^5	product	yield[a] %	purity[b] %
1	H	H	H	H	H	**3a**	83	>95
2	H	H	H	H	Br	**3b**	92	>95
3	H	H	H	H	Cl	**3c**	90	>95
4	H	H	H	H	F	**3d**	85	>95
5	H	H	H	H	OH	**3e**[c]	81	>95
6	H	H	H	H	OCH_3	**3f**[c]	80	>95
7	H	H	H	H	CH_3	**3g**	86	>95
8	H	H	Cl	H	Cl	**3h**	68	>90
9	H	CH_3	H	H	H	**3i**	51	>90
10	Cl	Cl	H	H	OCH_3	**3j**[c]	48	>85
11	H	H	H	OCH_3	OH	**3k**[c]	80	>90
12	H	H	H	$-OCH_2O-$		**3l**[c]	82	>90

[a] Yields of the crude product based on the loading of selenium bromide resin (Br, 1.01 mmol/g). [b] Determined by HPLC analysis. [c] The cyclization reactions were complete after 24 h.

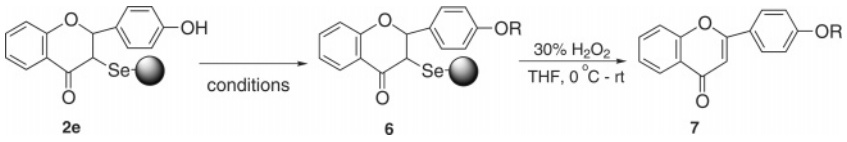
Table 3. Solid-Phase Synthesis of Substituted Flavonoids **5**



entry	RBr or $Ar_2I^+Br^-$	product	yield[a], %	purity[b], %
1	*n*-C_4H_9Br	**5a**	68	>85
2	*n*-$C_8H_{17}Br$	**5b**	66	>85
3	*i*-C_3H_7Br	**5c**	61	>85
4	$CH_2{=}CHCH_2Br$	**5d**	62	>90
5	BnBr	**5e**	56	>80
6	$(C_6H_5)_2IBr$	**5f**	41[c]	
7	$(4\text{-}Cl{-}C_6H_4)_2IBr$	**5g**	37[c]	

[a] Yields of the crude product based on the loading of selenium bromide resin (Br, 1.01 mmol/g). [b] Determined by HPLC analysis. [c] Isolated yield.

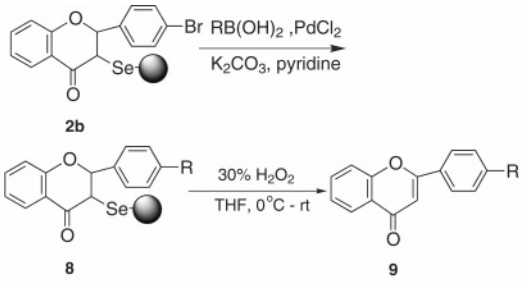
Table 4. Solid-Phase Synthesis of Flavonoids **7**



entry	conditions[a]	R	product	yield[b] %	purity[c] %
1	A	SO_2Ph	**7a**	63	>85
2	A	$SO_2C_6H_4CH_3$-*p*	**7b**	68	>85
3	A	$COCH_3$	**7c**	55	>80
4	A	COCH=CHPh	**7d**	66	>85
5	A	COPh	**7e**	45	>80
6	B	$PO(OEt)_2$	**7f**	60	>80

[a] A: RX, Et_3N, CH_2Cl_2, rt. B: $(EtO)_2POH$, CCl_4, dioxane, rt. [b] Yields of the crude product based on the loading of selenium bromide resin (Br, 1.01 mmol/g). [c] Determined by HPLC analysis.

Table 5. Solid-Phase Synthesis of 4′-Phenylflavonoid **9**

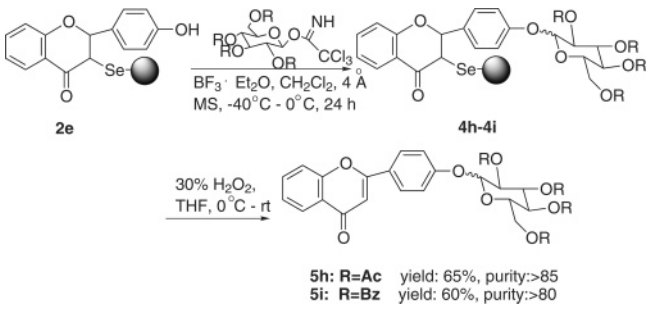


Entry	R	Product	Yield[a] (%)	Purity[b](%)
1	Ph	**9a**	58	>80
2	*p*-$CH_3OC_6H_4$	**9b**	60	>90
3	*p*-$CH_3C_6H_4$	**9c**	57	>95
4	*p*-ClC_6H_4	**9d**	50	>85
5		**9e**	50	>80
6		**9f**	46	>80
7		**9g**[c]	23[d]	–

[a] Yields of the crude product based on the loading of selenium bromide resin (Br, 1.01 mmol/g). [b] Determined by HPLC analysis. [c] The Suzuki coupling reaction was quenched after 48 h. [d] Isolated yield.

tion of cellular metabolism,[12a] flavonoid glycosides can be used to prevent and treat cardiovascular disease and cancer.[12b−12f] Our interest in achieving the synthesis of carbohydrate-containing structure stems from the propensity of sugar to improve the cellular targeting of flavonoids. The trichloroacetimidate of D-glucose was prepared by a three-step procedure.[13] As shown in Scheme 1, peracylated and perbenzoylated flavonoid glycosides **5h** and **5i** were synthesized in 65 and 60% yields by the treatment of resin **2e** with trichloroacetimidate of D-glucose in the presence of BF_3·Et_2O and 4-Å molecular sieves[14] and the subsequent oxidative cleavage of resins **4h** and **4i**. Results are summarized in Scheme 1.

Scheme 1. Solid-Phase Synthesis of Flavonoid Glycosides **5h** and **5i**



Resin **2e** can also easily undergo esterification with different kinds of acylation, sulfonylation, and phosphorylation reagents. Sulfonic esters of phenols are sufficiently stable to serve as potential lead structures for various types of drugs,[15] whereas the esters of phosphoric acid have wide bioactivities, play a vital role in many biological processes, and appear to undergo interconversion with great ease in living organisms.[16a−16d] In this process, resin **2e** was treated with sulfonyl chloride in CH_2Cl_2 at room temperature[17] to form sulfonate **6**, which afforded sulfonates **7** in 66 and 68% total yield, respectively, via the subsequent *syn*-selenoxide elimination **(**Table 4, entries 1−2). Acylation of resin **2e** can also be performed under the same conditions as sulfonation in 55 and 45% total yields, respectively (Table 4, entries 3−5). Phosphorylation reaction of resin **2e** was tested through a simplified Atheron−Todd reaction (Table 4, entry 6).[16e]

To expand the scope of the diversity of this method, we tested the Suzuki cross-coupling reaction of resin **2b** under the conditions recently developed by Tao et al.[18] Arylboronic acids reacted smoothly with resin **2b**, which was followed by *syn*-seleoxide elimination to give **9a**−**9f** in the combined yields of 46−60%. The Suzuki coupling reaction worked despite that R (in $RB(OH)_2$) is an aryl group with an electron-donating group or an electron-withdrawing group, although the reaction worked better when R was an aromatic group with an electron-donating group (entries 2−6, Table 5). The Suzuki coupling reaction with 3-trifluoromethyl-4-chloro-

phenyl boronic acid was incomplete, and the isolated yield of product **9g** was only 23% (entry 7, Table 5).

In summary, we have developed a solid-phase synthetic method for the preparation of flavonoids with good yields and purities. Further modifications, such as etherification, esterification, and Suzuki coupling to the resin flavonoids **2**, have also been demonstrated. The easy workup procedure provides the method that is well-suited for building the parallel libraries upon the basis of further transformation.

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Supporting Information Available. Experimental details and data of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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