Preparation of Chromane Derivatives *via* Indium-mediated Intramolecular Allylation Reactions

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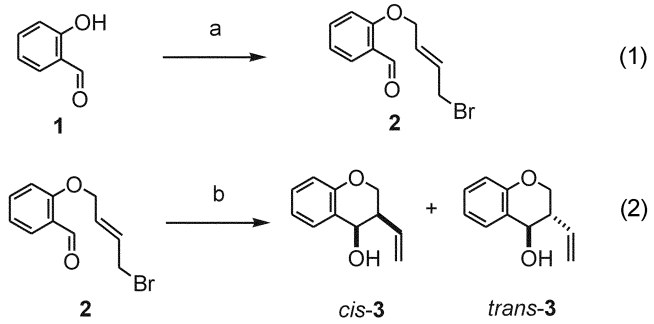
Chromane is one of the common structural parts found in many natural products.[1] We have already communicated the indium-mediated allenylation in one-pot fashion to construct chromane derivatives.[2] We have felt that indium-mediated allylation is also worth investigating in order to find out not only the possible difference in reactivity between allyl indium *vs*. propargyl indium but also the stereoselectivity difference in the indium-mediated cycliztion. We here wish to disclose our results on the intramolecular indium-mediated allylation to prepare chromanes.

The substrate **2**, a precursor for the cyclization, was prepared by the reaction of salicyladehyde (**1**) with 1,4-dibromo-2-butene in the presence of potassium carbonate as a base and potassium iodide (catalytic amount) in acetone at room temperature (Scheme 1).

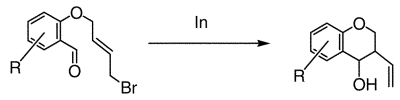


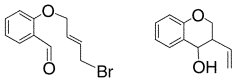
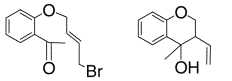
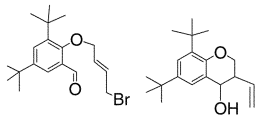
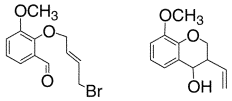
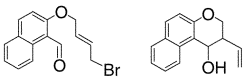
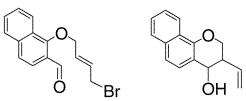
Scheme 1. Reagents and condtions: (a) (*E*)-1,4-dibromo-2-butene, K_2CO_3, KI (cat.), acetone, 6 h (69%) (b) indium, water/THF (3 : 1), 2 days, 23 °C (39%).

The indium-mediated cyclization of **2** was tested in various solvents such as THF, DMF, and CH_2Cl_2, and the desired cyclized product was obtained only in low yields even after long reaction time. When THF/water (THF : water = 3 : 1, *v/v*) was employed as a solvent system, the product was, however, obtained in 39% yield as a mixture of *cis* and *trans* isomers (*cis*/*trans* = 2 : 1). The stereochemistry of the products was determined by the NOE analysis and comparison with the ^{1}H NMR spectral data reported in the literature.[3] Fortunately, It was found that the presence of an acid (HCl) caused a remarkable effect on the reaction rate as well as on the yields of cyclization. HCl (2 eq based on indium) was effective although the isomeric ratio (*cis*/*trans*) remained unimproved. Under the condition of indium-mediated cyclization in water/THF as a solvent system in the presence of HCl (6 N, 2 eq) the reaction was completed in 30 min (83% yield). Similar favorable effect was observed when acetic acid (6 eq) was used as an additive. In order to test the generality of the indium-mediated allylation, we have prepared various salicylaldehyde derivatives. Table 1 shows the results of the intramolecular indium-mediated allylation with thus prepared salicylaldehydes under the condition we developed [water/THF = 3 : 1, HCl (2 eq)]. All the cyclizations were completed in less than 1 h and the corresponding chromanes were formed in reasonable yields.

It would be convenient if the substrate preparation (allylation of salicylaldehydes) and the indium-mediated

Table 1. Intramolecular allyation of various substrates[a]



entry	Reactant	Product	time (min)	yield (%)[b]	*cis*/*trans*[c]
1			30	83	2/1
2			45	87	2/1
3			45	56	1.2/1
4			40	69	2/1
5			50	65	4/1
6			50	84	2/1

[a]Reaction conditions: water/THF = 3 : 1 (*v*/*v*), indium (2 eq), HCl (2 eq), RT. [b]isolated yield. [c]determined by ^{1}H NMR

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cyclization to chromanes could be performed in succession without isolation of the intermediates. It has been known that acetone is an excellent solvent for the first step (allylation of salicylaldehydes) (Eq. 1, Scheme 1). This step, however, could not be conducted in water/THF which was used as an efficient solvent system in the indium-mediated intramolecular addition in many reported cases.[4] In order to achieve the one-pot reaction, we, therefore, needed to examine the solvents involved in the two steps. Among the solvents (other than acetone) tested for the first step (Eq. 1, Scheme 1), ethanol and DMF were good candidates for the common solvents for both steps. The yields were 67 and 54%, respectively, after 24 h. Other solvents such as CH_2Cl_2, CH_3CN, and THF did not provide any product. For the second step, that is, the indium-mediated cyclization (Eq. 2, Scheme 1) proceeded in the presence of HCl efficiently only in EtOH [EtOH/0.1 N HCl (1 : 4) was used]. No reaction was observed in other solvents such as acetone and CH_3CN. Interestingly, in DMF the reaction did proceed to provide the desired product. The yield was, however, much lower. In this case, acetic acid was more efficient than HCl (2 eq) although increased amount of acetic acid (10 eq) had to be used. This makes an interesting contrast to the indium-mediated allenylation.[2] The one-pot preparation of the chromane derivatives from salicylaldehydes and 1,4-dibromo-2-butene was carried out in two possible solvents, that is, in DMF and EtOH.

As expected, EtOH/0.l N HCl (4 : 1, *v*/*v*) provided a better yield than DMF (with 10 eq of AcOH). As a result, EtOH was found to be the best common solvent for both steps (Eq 2 and 3, Scheme 1). The alkylation of 1,4-dibromo-2-butene was performed in EtOH.[5] Table 2 summarized the results for the one-pot preparation of chromane derivative under the reaction conditions developed.

In conclusion, we have shown that the synthesis of chromane derivatives can be achieved by the indium-mediated intramolecular allylation. It is also possible to prepare chromanes efficiently by the one-pot reaction starting from salicylaldehydes and 1,4-dibromobutene. For this efficient transformation, EtOH was selected as a reaction medium.

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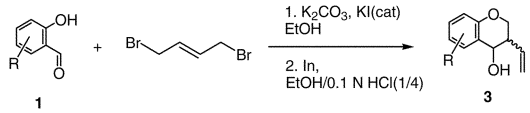
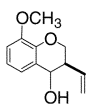
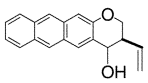
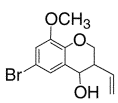
Table 2. One-pot preparation of chromanes[a]



entry	Product	yield (%)[b]	*cis*/*trans*[c]
1		56	2/1
2		43	2/1
3		30	2/1
4		52	3/1

[a]Reaction conditions: indium (2 eq), RT. [b]isolated yield. [c]determined by ^{1}H NMR

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5. Typical procedure: **Preparation of 3-vinylchroman-4-ol** (Table 2, entry 1). To a solution of potassium carbonate (66 mg, 0.48 mmol) and potassium iodide (6 mg, 0.004 mmol) in ethanol (1 mL) was added salicylaldehyde (49 mg, 0.40 mmol) and 1,4-dibromo-2-butene (85 mg, 0.40 mmol). The solution was stirred at room temperature for 24 h until the reaction was completed. The solution was neutralized by adding 0.1 N HCl solution (4 mL). After addition of indium (92 mg, 0.80 mmol) the resulting solution was stirred for 1 h. After the reaction was completed, the solution was extracted with ether (20 mL × 2). The organic layer was dried ($MgSO_4$) and concentrated. Flash chromatography (hexane : ethyl acetate = 7 : 1) provided the desired cylized products, (*Z*)-3-vinylchroman-4-ol (13 mg, 19%) and (*E*)-3-vinylchroman-4-ol (26 mg, 37%) as colorless oils.
(*E*)-3-vinylchroman-4-ol: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, 1H, *J* = 7.6, 1.6 Hz, ArH), 7.22 (dt, 1H, *J* = 7.1, 1.7 Hz, ArH), 6.93 (dt, 1H, *J* = 8.2, 1.0 Hz, ArH), 6.86 (d, 1H, *J* = 8.2 Hz, ArH), 5.94 (ddd, 1H, *J* = 7.4, 10.4, 17.4 Hz, -C*H*=CH$_2$), 5.36 (d, 1H, *J* = 10.1 Hz, CH=C*H*H), 5.29 (d, 1H, *J* = 17.4 Hz, CH=C*H*H), 4.72 (m, 1H, C*H*OH), 4.24 (t, 1H, *J* = 10.4 Hz, -OC*H*HC), 4.18 (dd, 1H, *J* = 11.1, 3.8 Hz, -OCH*H*C), 2.77 (m, 1H, -C*H*-CH=CH$_2$), 1.93 (br, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.4, 134.1, 130.3, 130.2, 124.2, 121.0, 119.4, 117.1, 66.4, 65.3, 42.9; HRMS: *m/z* Calcd for $C_{11}H_{12}O_2$: 176.0837. Found: 176.0836.
(*Z*)-3-vinylchroman-4-ol: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, 1H, *J* = 7.6, 1.2 Hz, ArH), 7.21 (dt, 1H, *J* = 7.5, 1.6 Hz, ArH), 6.94 (dt, 1H, *J* = 7.4, 1.0 Hz, ArH), 6.83 (d, 1H, *J* = 8.2 Hz, ArH), 5.73 (ddd, 1H, *J* = 7.4, 10.5, 17.7 Hz, -C*H*=CH$_2$), 5.29 (d, 1H, *J* = 17.3 Hz, CH=C*H*H), 5.23 (d, 1H, *J* = 10.5 Hz, CH=CH*H*), 4.60 (m, 1H, C*H*OH), 4.30 (dd, 1H, *J* = 11.2, 3.2 Hz, -OC*H*HC), 4.09 (dd, 1H, *J* = 11.1, 7.2 Hz, -OCH*H*C), 2.65 (dddd, 1H, *J* = 7, 7, 7, 3.2 Hz, -C*H*-CH=CH$_2$), 2.09 (br, 1H, OH); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 154.5, 135.2, 129.9, 129.3, 123.9, 121.2, 118.8, 117.0, 66.5, 66.3, 44.8; HRMS: *m/z* Calcd for $C_{11}H_{12}O_2$: 176.0837. Found: 176.0834.