Solid-Phase Synthesis of Benzopyran Building Blocks *via* Highly Efficient Hydroxy-Alkoxylation

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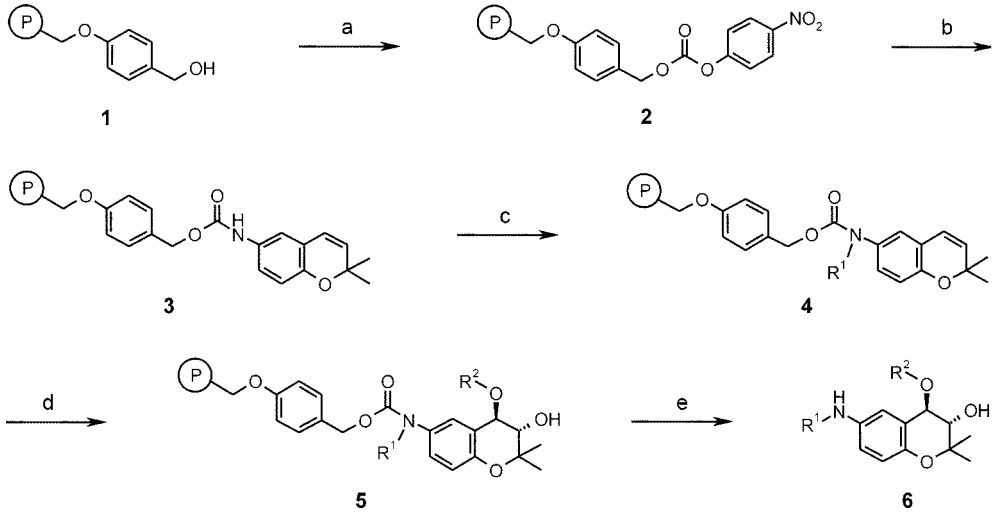
Solid-phase organic synthesis has emerged as a powerful technique in generating combinatorial libraries of small organic molecules useful for drug discovery.[1] Heterocyclic compounds provide scaffolds on which pharmacophores can be arranged to yield potent and selective drugs. A variety of heterocycles has been synthesized on solid support.[2] In our research program for the development of potassium channel activators and antioxidants, we needed to develop synthetic strategies and chemistries applicable in a combinatorial approach to the various benzopyran derivatives.[3] Herein, we would like to report our findings about a facile hydroxy-alkoxylation condition of the chromene derivatives **3** on a solid-phase where the normal reaction condition failed to produce the desired intermediate epoxide to generate subsequently the 3-hydroxy-4-alkoxy substituted benzopyran library (Scheme 1).

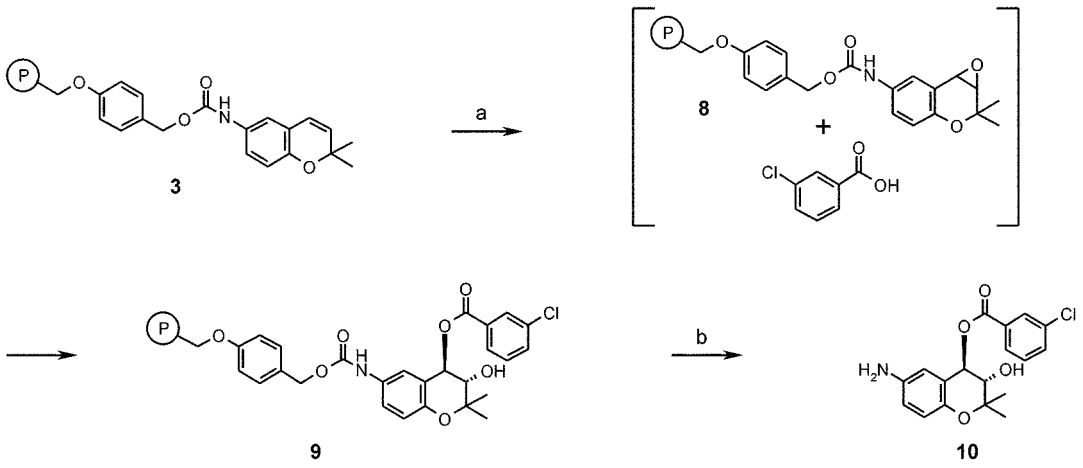
We selected the Wang resin **1** as a polymer support since the hydroxyl group in the Wang resin is useful in the introduction of 6-amino-chromenes 7 through the carbamate linker which also serves as an efficient protection group for the amino group against the subsequent oxidation and alkylation reaction.[4] The benzopyran derivatives **6** were finally liberated from the resin by trifluoroacetic acid (TFA). The carbamate resin **3** was synthesized in a two-step procedure starting from Wang resin as follows (Scheme 1).

In the first step, the 4-nitrophenyl carbonate resin **2** was prepared by adding pyridine in CH_2Cl_2 to the Wang resin **1** in the presence of *p*-nitrophenyl chloroformate in CH_2Cl_2.[5] The reaction of carbonate resin **2** with 6-amino-2,2-dimethyl chromene and *N,N*-diisopropylethylamine (DIPEA) in *N,N*-dimethylacetamide (DMA) afforded the carbamate resin **3** confirmed by the appearance of the carbamate peak at 1760 cm^{-1} in the attenuated total reflection Fourier transform infrared (ATR-FTIR) spectrum. Subsequently various alkyl substituents were introduced by neucleophilic addition reaction with alkyl halides and lithium *t*-butoxide in dimethyl sulfoxide (DMSO),[6] and the progress of the reaction was monitored by the shift of the carbamate peaks from 1723 cm^{-1} of **3** to 1700 cm^{-1} of **4** in ATR-FTIR spectrum.

With the carbamate **3** in hand, we examined the epoxidation of **3** under normal oxidation conditions with *m*-chloroperbenzoic acid (*m*-CPBA) in CH_2Cl_2.[7] However, under this condition we found that the *m*-chlorobenzoic acid



Scheme 1. *Reagents and conditions*: (a) *p*-nitrophenyl chloroformate, pyridine, CH_2Cl_2; (b) 6-amino-2,2-dimethyl chromene **7**, DIPEA, DMA; (c) alkyl or benzyl halide, *t*BuOLi, DMSO; (d) *m*-CPBA, alcohol, CH_2Cl_2; (e) TFA:CH_2Cl_2 (1 : 3). **5**, and **6** are racemates.



Scheme 2. *Reagents and conditions*: (a) *m*-CPBA, CH_2Cl_2; (b) 25% TFA, CH_2Cl_2.

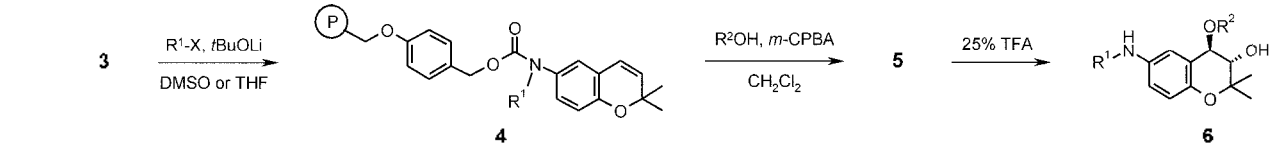
incorporated adduct resin **8** was mostly formed (Scheme 2). This is probably due to the presence of excessive *m*-chlorobenzoic acid which attacked the initially formed epoxide resin **8** preferentially.

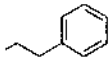
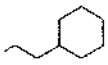
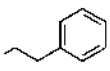
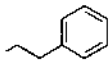
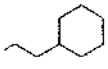
In order to solve this problem, we attempted various oxidation conditions such as oxone, dimethyl dioxirane, hydrogen peroxide, *t*-butyl hydrogen peroxide and sodium perchlorate in dichloromethane without a success to obtain the desired epoxide resin **8**. The treatments of the polymer bound olefine **3** with these oxidants in water or acetone also failed to produce **8**. The failure is most likely due to the poor resin swelling by polar solvents such as water or acetone.

Therefore, we decided to scrutinize the *m*-CPBA condition more carefully and particularly the solvent system. After examining various solvent systems, we found that the two-phase solvent system of chloroform and saturated aqueous $NaHCO_3$ was a suitable condition, and this result was reported on the previous paper.[8]

However, the epoxidation condition under the two-phase solvent system has a limitation which is not appropriate for a large scale (>1 g resin weight) reaction on the solid-phase. Therefore, we needed to develop more facile epoxidation

Table 1.



Compd	R^1	R^2	Yield (%)*	Compd	R^1	R^2	Yield (%)*
6a	H	Me	81	**6n**	4-Methoxy-Bn	*i*Pr	45
6b	Bn	Me	62	**6o**	4-Methoxy-Bn	Bu	66
6c	Bn	*i*Pr	35	**6p**	4-Methoxy-Bn	Bn	54
6d	Bn	Bu	53	**6q**	4-Methoxy-Bn		51
6e	Bn	Bn	58	**6r**	4-Methoxy-Bn		53
6f	Bn		44	**6s**	4-Methoxy-Bn	Et	67
6g	Pentyl	Me	47	**6t**	4-F-Bn	Me	79
6h	3-F-Bn	Me	53	**6u**	4-F-Bn	*i*Pr	43
6i	Me	Me	63	**6v**	4-F-Bn	Bu	74
6j	4-*t*Bu-Bn	Me	45	**6w**	4-F-Bn	Bn	62
6k	4-Me-Bn	Me	59	**6x**	4-F-Bn		56
6l	4-F-Bn	Me	58	**6y**	4-F-Bn		57
6m	4-Methoxy-Bn	Me	74	**6z**	4-F-Bn	Bn	71

*Three-step overall yield from carbamate resin **3** (the loading capacity of resin **3** in 0.5 mM g).

condition or consecutive epoxidation-addition reaction which can be useful for a large scale reaction on the solid-phase. We scrutinized the consecutive neucleophilic additon reactions of carbamate resin **4** with nucleophiles immediately followed by *m*-CPBA epoxidation. After examining various neucleophiles, we found that alkyl alcohols, benzyl alcohols and substituted benzyl alcohols provided the hydroxy-alkoxide resin **5** in high yield without the formation of **9**. The progress and yield of this hydroxy-alkoxylation reaction were monitored by measuring the relative amount of **10** over **6** which were released from the resin **9** and **5** by treating the resin with 25% TFA for 3 hrs. respectively.

In a typical consecutive hydroxy-alkoxylation *via m*-CPBA epoxidation procedure, the chromene resin **4a** (50.0 g, 27.5 mmol), dissolved in 200 mL (1 : 1) of MeOH and CH_2Cl_2, was added to *m*-CPBA (67.6 g, 70%, 275.0 mmol) and the mixture was shaken at 40 °C for 12 hrs. The resin was filtered, washed with CH_2Cl_2, DMF, and MeOH and then dried over a vaccum overnight.

Finally, we carried out the cleavage reaction of the polymer bound hydroxyl-methoxide **5a** with 25% TFA in CH_2Cl_2 to produce the desired benzopyran products **6a** in high yields without significant contamination of by-products. The representative results are shown in Table 1.

In conclusion, we have demonstrated that the consecutive nucleophilic addition *via m*-CPBA epoxidation is suitable for the large scale of hydroxy-alkoxylation of polymer bound chromenes **4** to minimize the formation of the by-product **9**. The 26 hydroxyl-alkoxide benzopyran analogs **6** were prepared by the three step procedure from **3** *via m*-CPBA epoxidation reaction as a key step. The hydroxy-alkoxide **5** can serve as useful intermediates to react with various electrophiles such as alkyl halides, acyl halides. And the remaining hydroxy group can also be utilized for further combination with various carboxylic acids to prepare diverse chemical libraries for biological evaluation.

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