Solid-Phase Synthesis of Benzopyran Derivatives *via* Highly Efficient Epoxidation Using Two-Phase Solvents

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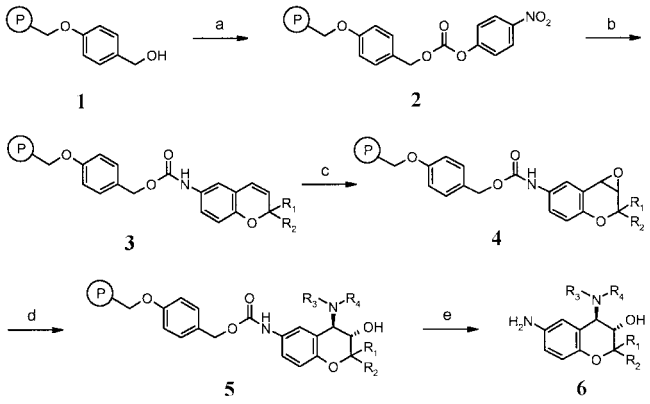
Solid-phase organic synthesis has emerged as a powerful technique in generating combinatorial libraries of small organic molecules useful for drug discovery.[1] Heterocyclic compounds provide scaffolds on which pharmacophores can be arranged to yield potent and selective drugs. A variety of heterocycles have been synthesized on solid support.[2] In our research program for the development of potassium channel activators, 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 new epoxidation condition of the chromene derivatives **3** on a solid-phase where the normal reaction condition failed to produce the desired epoxide products. We then report a successful application of the epoxides **4** to generate the 3-hydroxy-4-amino substituted benzopyran library (Scheme 1).

We selected the Wang resin **1** as a polymer support, as the hydroxy group of the Wang resin is useful in the introduction of 6-amino-chromenes **6** through the carbamate linker which also serves as an efficient protection group for the amino group against the subsequent oxidation and alkylation reactions.[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).



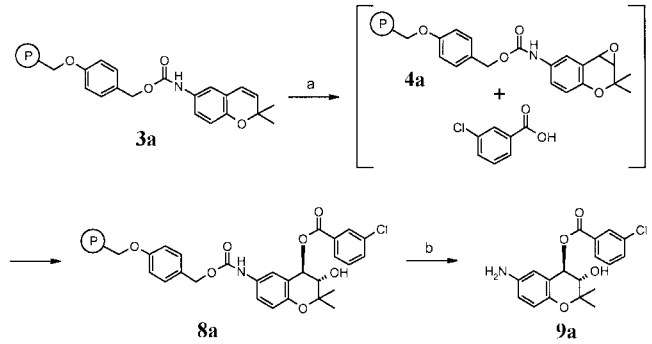
Scheme 1. *Reagents and conditions*: (a) *p*-nitrophenyl chloroformate, pyridine, CH_2Cl_2; (b) 6-amino-2,2-dimethyl chromene **7**, DIPEA, DMA; (c) *m*-CPBA, $CHCl_3$: sat. aqueous $NaHCO_3$ (9 : 1); (d) 2 equiv. $Mg(ClO_4)_2$, 4 equiv. R_3R_4NH, CH_3CN; (e) TFA : CH_2Cl_2 (1 : 3), 4, 5, and 6 are racemates.

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*-diisopropylethylamine (DIPEA) in *N,N*-dimethylacetamide (DMA) afforded the carbamate resin **3** and the progress of the reaction was verified by the complete disappearance of the carbonate peak at 1760 cm^{-1} in the IR spectrum.

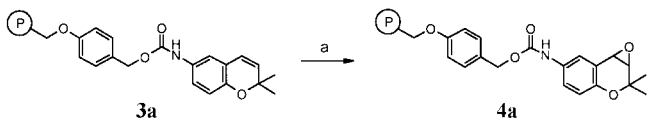
With the carbamate **3a** in hand, we examined the epoxidation of **3a** under normal oxidation conditions with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane.[6] How-ever, under this condition we found that the *m*-chlorobenzoic acid added adduct resin **8a** was mostly formed (Scheme 2). This is probably due to the presence of excessive *m*-chlorobenzoic acid which attacked the initially formed epoxide resin **4a** preferentially. In order to resolve this problem we tried to search for other oxidation conditions.

We examined various oxidants such as oxone, dimethyl dioxirane, hydrogen peroxide, *t*-butyl hydrogen peroxide and sodium perchlorate[6] in dichloromethane and failed to obtain the desired epoxide resin **4a**. The treatment of the polymer bound olefine **3a** with these oxidants in water or acetone also failed to produce **4a**. 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, particularly the solvent system. After examining various solvent systems and two-phase



Scheme 2. *Reagents and conditions*: (a) *m*-CPBA, CH_2Cl_2; (b) 20% TFA, CH_2Cl_2.



Scheme 3. *Reagents and conditions*: (a) *m*-CPBA (2.2 eq), $CHCl_3$: sat. aqueous $NaHCO_3$ (9 : 1).

solvent systems, we found that the two-phase solvent system comprised of chloroform and saturated aqueous $NaHCO_3$ was quite satisfactory. Under this condition the desired epoxide resin **4a** was obtained in good yield without the formation of **8a**. We assumed that the success of this reaction was due to the basic aqueous solution's ability to remove excess *m*-chlorobenzoic acid quite effectively. This explanation was well supported by the fact that the use of bases such as triethylamine, DIPEA, NaOH, and $NaHCO_3$ without water[6] did not produce the desired epoxidation product. The progress and yield of this *m*-CPBA epoxidation reaction were monitored by measuring the amount of **9a** and the desired products **6a** which were released from the resin **8a** and **5a** by treating the resin with 25% TFA for 3 hrs, respectively.

In a typical epoxidation procedure, the chromene resin **3a** (1.0 g, 1.1 mmol), dissolved in 20 mL of chloroform, was added to *m*-CPBA (455.6 mg, 2.4 mmol) and the mixture was stirred at 0 °C. After 5 min., 2 mL of saturated aqueous $NaHCO_3$ was added and the mixture was stirred at room temperature for 12 hrs. The resin was filtered and washed with saturated aqueous $NaHCO_3$ solution, water, water/MeOH, MeOH and dichloromethane. The resin was then dried under a vacuum overnight.

Finally we carried out the ring opening reaction of the polymer bound epoxide **4a** with nine amines to produce the desired benzopyrane products **6** in good overall yields without significant contamination of the by-products (Table 1).

In conclusion, we have demonstrated that the two-phase solvent system for *m*-CPBA oxidation is suitable for the epoxidation of polymer bound chromenes **3** to minimize the formation of the by-product **8a**. The epoxides **3** can serve as useful intermediates for reacting with various nucleophiles, such as carboxylic acids, alcohols and thiols etc. The hydroxyl compounds **6** can also be used for further combination with acylating agents to preparing diverse chemical libraries for biological evaluation.

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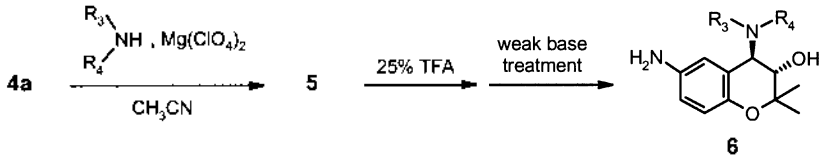
Table 1.



	R_3	R_4	Yield (%)*		R_3	R_4	Yield (%)*
6a	4-Ethylphenyl	H	32	**6f**	4-Methoxy phenyl	H	33
6b	Phenyl	Et	26	**6g**	2-Methoxy phenyl	H	27
6c	Benzyl	H	22	**6h**	2,4-Dimethoxy phenyl	H	29
6d	Allyl	H	20	**6i**	3-Nitrophenyl	H	25
6e	Benzyl	Me	13				

*Five-step overall yield from Wang resin (the Wang resin loading capacity is 1.1 mM/g)