Rearrangement of epoxides to allylic alcohols in the presence of reusable basic resins

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We have modified Merrifield's resin to provide polymers containing secondary amine groups. Lithiation of the solids gives strongly basic yet poorly nucleophilic resins useful for rearrangement of epoxides to their corresponding allylic alcohols. The resins are easy to handle, non-volatile, non-toxic, and are easily recovered and reused, providing environmental and economic benefits that might have commercial viability.

KEY WORDS: epoxide; modified basic Merrifield's resin; rearrangement; allylic alcohols; heterogeneous reactions.

1. Introduction

Epoxides are versatile intermediates for various organic transformations due to their ready availability and easy conversions to many organic compounds [1-4]. The rearrangement of epoxides to produce allylic alcohols is one such application [5]. It is known to occur *via* both α- and β-deprotonation processes [6], the latter of which

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involves a simple β-elimination reaction and is generally preferred (Scheme 1). Several catalytic systems have been developed for the rearrangement of epoxides to allylic alcohols [7-11]. These include potassium *tert*-butoxide in dimethylsulfoxide at 45 °C [12], *tert*-butyllithium in pentane at low temperature [13] or under reflux conditions [14], lithium dialkylamides in hexane or diethyl ether [15-25], silicon reagents [26,27], aluminium reagents [28-32] and metal supported on metal oxides and metal sulfates at high temperatures [33].

Unfortunately, most of these reagents create a number of environmental disadvantages, such as the production of large quantities of toxic waste, the need to be carried out at high temperatures for long reaction times, or the use of bases that cannot be recycled and reused. In recent years major efforts have been made to find cleaner replacements for processes that are not environmentally friendly [34,35]. The use of solid catalysts can overcome many of the limitations associated with traditional processes [36,37]. For example, we have shown that solid catalysts [38,39] can have advantages in alkylation [40], acylation [41,42], methanesulfonylation [43], bromination [44], chlorination [45] and nitration [46,47] of aromatic compounds under electrophilic conditions. Recently we have also investigated the rearrangement reactions of epoxides over acidic solid catalysts under mild conditions, which produce carbonyl compounds [48]. Therefore, it was also of interest to develop solid bases that could be used for rearrangement reactions of epoxides to give allylic alcohols.

Lithium dialkylamides [15-25] are the most powerful and among the most successful of bases reported for use as catalysts for rearrangement of various epoxides to the corresponding allylic alcohols, and are easily prepared from the reactions of an alkyllithium with the appropriate dialkylamine. In order to gain the benefit of a lithium dialkylamide as a heterogeneous catalyst, we decided to modify Merrifield’s resin by replacing the chlorine atom by an alkylamino, cycloalkylamino or arylamino group. It was hoped that the newly modified basic Merrifield’s resins would provide advantages over their homogeneous counterparts, such as ease of workup, higher yields, enhanced product selectivity and easy recovery and reuse of the resin. We now report our results on the rearrangement of epoxides over such reusable resins.

2. Experimental

2.1. Materials

Chemicals were purchased from Aldrich Chemical Company and used without further purification. *tert*-Butylithium was obtained from Aldrich Chemical Company and was estimated prior to use by the method of Watson and Eastham [49]. THF was distilled from sodium benzophenone ketyl. Other solvents were purified by standard procedures [50,51].

2.2. Analysis and characterisation of the products

Product mixtures from the rearrangement reactions of epoxides were subjected to gas chromatography on a Philips PU 4400 gas chromatograph, fitted with an HP-1 (100% dimethylpolysiloxane; 30 m, 0.32 mm ID) column. The GC conditions used for analysis were: 40 °C for 0.2 min, ramped to 150 °C at 10 °C/min and held for 0.2 min. The injection temperature was 300 °C and the detection temperature 300 °C. Tetradecane was used as an internal standard.

Cyclohexene oxide, α-pinene oxide, cyclopentene oxide, cyclooctene oxide and 1-phenylpropene oxide are commercial materials and were used without further purification.

2.3. *Typical experimental procedure for the modification of Merrifield's resin to produce modified resin **2** according to Scheme 2*

All reactions were carried out under a nitrogen atmosphere in a 100 ml two necked round bottomed flask equipped with a magnetic stirrer. In a typical experiment, a solution of *tert*-butyllithium in pentane (20 ml, 1.7 M, 34 mmol) was added in a dropwise manner to a cooled solution (-78 °C) of primary amine (34 mmol) in THF (30 ml). The mixture was stirred for 30 min at –78 °C, after which the cooling bath was removed and the mixture was slowly warmed to room temperature. The milky suspension was transferred *via* a wide bore double-ended needle to a chilled (-78 °C) suspension of Merrifield's resin (5.0 g, 8.5 mmol of Cl), which had been previously swollen in dry THF (20 ml). The darkened mixture was stirred for a further 30 min at –78 °C and then slowly allowed to warm to room temperature and stirred overnight. Methanol (30 ml) was added and the mixture was stirred for 30 min. The solvents were decanted from the resin, which was then washed with a mixture of benzene/methanol (100 ml, 1:1 by volume) and then filtered and dried.

2.4. *Experimental procedure for the rearrangement of epoxides to the corresponding allylic alcohols in the presence of resins (**2**) and tert-butyllithium*

The appropriate modified Merrifield's resin (**2**; 5.8 mmol) was placed in a 100 ml dry two necked round bottomed flask equipped with a double surface condenser and a magnetic stirrer and the whole system was kept under a nitrogen atmosphere. Dry THF (50 ml) was added and the mixture was stirred for 5 min to swell the resin. The mixture was then cooled to –78 °C and *tert*-butyllithium (4.3 ml, 1.7 M, 7.3 mmol) was added dropwise to produce the corresponding lithiated resin (**3**), observable by its brown colouration. The reaction mixture was stirred at –78 °C for 30 min and then for 90 min at room temperature. A solution of epoxide (3.3 mmol) in dry THF (5 ml) was added and the mixture was heated under reflux under nitrogen for 3 h (α-pinene oxide), 8 h (cyclohexene oxide) or 24 h (cyclopentene oxide, cyclooctene oxide and 1,2-epoxy-1-phenylpropene). The reaction mixture was then filtered and the solid was extracted by reflux with fresh diethyl ether (3 x 15 ml). The combined filtrates were concentrated to *ca*. 5 ml and a mixture of water (10 ml) and diethyl ether (15 ml) was added. The organic layer was separated, dried ($MgSO_4$), filtered and concentrated under reduced pressure. The product mixture was analysed and quantified by GC.

The resin was stirred with methanol for 15 min, filtered, washed with methanol and then dried under reduced pressure at 65 °C for 24 h.

3. Results and discussions

Initially, we investigated the replacement of the chloride of Merrifield's resin by a *tert*-butylamino group (Scheme 2; R = *t*-Bu). It was felt that this would provide about the same degree of steric hindrance about the nitrogen as in lithium diisopropylamide (LDA), which has been commonly applied for epoxide to allylic alcohol rearrangements. A 1:1 molar ratio of *tert*-butyllithium and *tert*-butylamine in anhydrous THF was added to swollen Merrifield resin (**1**) in THF at –78 °C, then stirred at room temperature overnight. The solid resin was filtered, washed with a variety of solvents and dried at 65 °C to give the modified resin **2a**. The functional yield of **2a** was determined by titration with acid and found to be only 44% (Table 1; entry 1). In order to test the generality of the procedure, various modified Merrifield's resins **2b-e** were prepared by similar processes, but involving cyclohexylamine, aniline, 4-chloroaniline and 4-methylaniline (Scheme 2) instead of *tert*-butylamine. The functional yields obtained are given in Table 1.

As can be seen from Table 1, the functional yields were quantitative in most cases (97-99%), the reaction accommodating various substituents (aliphatic, alicyclic and aromatic) on the amine nitrogen. The reaction is efficient and fairly general under mild conditions, which renders it attractive for organic synthesis. However, when *tert*-butylamine was used in the reaction, only a moderate yield of **2a** (44%) was obtained.

With a variety of modified Merrifield's resins (**2**) available, our attention was next turned to their deprotonation by base and use of the deprotonated resin (**3**) for rearrangement of cyclohexene oxide (**4**). Addition of *t*-BuLi to a suspension of various resins **2** in anhydrous THF at –78 °C, followed by addition of cyclohexene oxide (**4**), gave 2-cyclohexen-1-ol (**5**; Scheme 3). The yields of **5** with different resins are shown in Table 2. The results indicate that the reaction was successful in the presence of a range of resins **2**. It was found that the yield of **5** was 83% after 8 h when resin **2b** was used (Table 2; entry 2). However, the lowest yield (53%) was obtained when resin **2a** was used (entry 1). It was found that resins **2c-e** gave moderate to good yields of **5** in the range of 58-64% (entries 3-5) under similar reaction conditions.

In view of the success with the rearrangement of **4** over resins **2**, the rearrangement of α-pinene oxide (**6**) over resins **2** in THF was also tried (Scheme 4) under conditions identical to those used for **4** except for the reaction time. The reactions were successful and produced the corresponding allylic alcohol **7** after 3 h. The yields obtained are recorded in Table 3. The trends in the results were consistent with those reported in Table 2 for the rearrangement of **4**. Clearly, the highest yield of

7 (93%) was obtained with resin **2b** (Table 3; entry 2). However, the lowest yield (33%) was obtained with **2a** (entry 1). Again, it was found that resins **3c-e** gave moderate to good yields (59-69%) of **7** (entries 3-5). Therefore, resin **2b** was considered to be the most useful for the rearrangement of epoxides and further studies made use of this resin particularly.

Samples of resins **2** were recovered from the reactions depicted in Schemes 3 and 4 and reused in rearrangement reactions identical to those from which the samples were recovered (rearrangement of **4** and **6**). The yields of **5** and **7** obtained showed that resins **2** could be reused at least four times with no reduction in the yields of products.

In view of the success with resin **2b**, our attention was next turned to the rearrangement of cyclopentene oxide (**8**) over resin **2b** in THF (Table 4; entries 1-3). It was found that the yield of the corresponding allylic alcohol **9** was only 10% after 2 h (entry 1), so we attempted to increase the yield of **9** by increasing the reaction time. On increasing the reaction time the yield of **9** increased to 20% after 4 h (entry 2) and to 30% after 24 h (entry 3). Clearly, the majority of the reaction occurred within the first 4 h and only an extra 10% was produced over the next 20 h. In addition, after 24 h the proportion of side products had become significant. For example, cyclopentanone was obtained in 14% yield after 24 h. Therefore, it would seem that increasing the reaction time too far is not beneficial.

Similarly, rearrangement of cyclooctene oxide (**10**) over resin **3b** in THF (Table 4; entries 4-6) gave the corresponding allylic alcohol **11** in only 10% yield after 2 h (entry 4). However, on increasing the reaction time to 4 h the yield of **11** increased to 21% (entry 5), while after 24 h the yield was 76% (entry 6). In addition, the yield of by-products was very low.

Finally, rearrangement of 1-phenylpropene oxide (**12**) over resin **3b** in THF was attempted (Table 4; entries 7 and 8). It was found that the yield of the corresponding allylic alcohol **13** was 50% after 2 h (entry 7) and increased only to 52% after 24 h (entry 8). Clearly, the majority of the reaction occurred within the first 2 h and little further reaction took place in the next 22 h. In addition, after 24 h the proportion of other products had become significant.

4. Conclusion

Procedures have been developed for the modification of Merrifield's resin to produce solid bases and their use for the efficient and selective synthesis of allylic alcohols. Reasonable yields of allylic alcohols were obtained. Furthermore, the modified resins can be easily regenerated and reused to give results similar to those obtained with a fresh sample of the catalyst.

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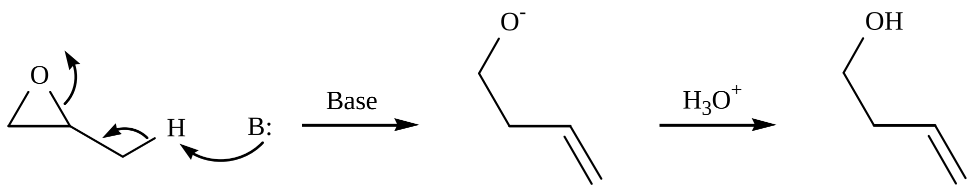
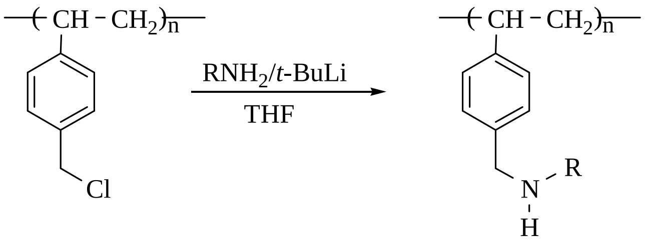
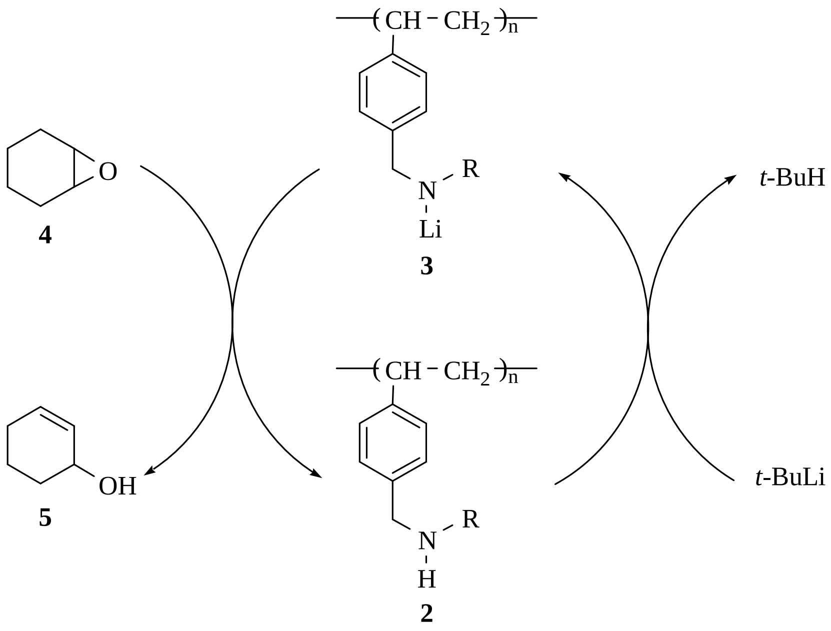


Scheme 1. Rearrangement of an epoxide *via* β-elimination under basic conditions.

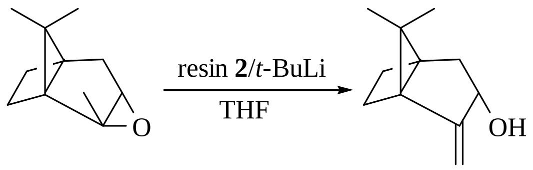


1 **2**

Scheme 2. Synthesis of modified Merrifield resins (**2**).



Scheme 3. Rearrangement of cyclohexene oxide (**4**) in the presence of **2** and *t*-BuLi.



6 **7**

Scheme 4. Rearrangement of α-pinene oxide (**6**) in the presence of **2** and *t*-BuLi

Table 1

Synthesis of modified Merrifield resins **2** according to Scheme 2[a]

Entry	Modified resin **2**	R	Functional yield (%)[b]
1	**2a**	*t*-Bu	44
2	**2b**	cyclohexyl	99
3	**2c**	Ph	98
4	**2d**	4-ClC_6H_4	98
5	**2e**	4-MeC_6H_4	97

[a] A solution of *t*-BuLi (20 ml, 1.7 M, 34.0 mmol) was added to a solution of amine (34.0 mmol) in THF (30 ml) then the mixture was stirred for 30 min at -78 °C. The mixture was transferred to a cold (-78 °C) suspension of **1** (5.0 g; 8.5 mmol of Cl) in THF (20 ml). The mixture was warmed up to room temperature, stirred overnight and the solid resin was washed with a variety of solvents and dried.

[b] Functional yield % was calculated by titration of **2** with HCl (0.05 M) solution.

Table 2

Rearrangement of cyclohexene oxide (**4**) over various resins **2** according to Scheme 3[a]

Entry	Resin **2**	R	Yield (%)[b]
1	**2a**	*t*-Bu	53
2	**2b**	cyclohexyl	83
3	**2c**	Ph	60
4	**2d**	4-ClC_6H_4	58
5	**2e**	4-MeC_6H_4	64

[a] *tert*-Butyllithium (4.3 ml, 1.7 M, 7.3 mmol) was added to a cooled (–78 °C) resin (**2**; 5.8 mmol) in THF (50 ml) and stirred for 30 min and then for 90 min at room temperature. A solution of **4** (0.32 g, 3.3 mmol) in dry THF (5 ml) was added and the mixture was heated under reflux under nitrogen for 8 h. The reaction mixture was worked-up and quantified by GC.

[b] Calculated from GC using tetradecane as an internal standard.

Table 3

Rearrangement of α-pinene oxide (**6**) over various resins **2** according to Scheme 4[a]

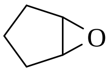
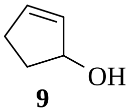
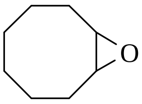
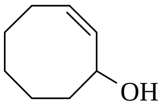
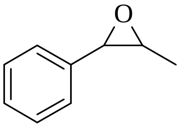
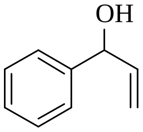
Entry	Resin **2**	R	Yield (%)[b]
1	**2a**	*t*-Bu	33
2	**2b**	cyclohexyl	93
3	**2c**	Ph	65
4	**2d**	4-ClC_6H_4	59
5	**2e**	4-MeC_6H_4	69

[a] *tert*-Butyllithium (4.3 ml, 1.7 M, 7.3 mmol) was added to a cooled (–78 °C) resin (**2**; 5.8 mmol) in THF (50 ml) and stirred for 30 min and then for 90 min at room temperature. A solution of **6** (0.50 g, 3.3 mmol) in dry THF (5 ml) was added and the mixture was heated under reflux under nitrogen for 3 h. The reaction mixture was worked-up and quantified by GC.

[b] Calculated from GC using tetradecane as an internal standard.

Table 4

Rearrangement of epoxides **8**, **10** and **12** over resin **2b** in the presence of *t*-BuLi[a]

Entry	Epoxide	Allylic alcohol	Reaction Time (h)	Yield (%)
1	 **8**	 **9**	2	10
2			4	20
3			24	30[c]
4	 **10**	 **11**	2	9
5			4	21
6			24	76
7	 **12**	 **13**	2	50
8			24	52[c]

[a] *tert*-Butyllithium (4.3 ml, 1.7 M, 7.3 mmol) was added to a cooled (–78 °C) resin (**2b**; 5.8 mmol) in THF (50 ml) and stirred for 30 min and then for 90 min at room temperature. A solution of **8**, **10** or **12** (3.3 mmol) in dry THF (5 ml) was added and the mixture was heated under reflux under nitrogen for the stated period. The reaction mixture was worked-up and quantified by GC.

[b] Calculated from GC using tetradecane as an internal standard.

[c] The proportion of side products had become significant.