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Asymmetric Glycolate Alkylation Reactions in the Solid Phase Using 2-Imidazolidinone Chiral Auxiliary

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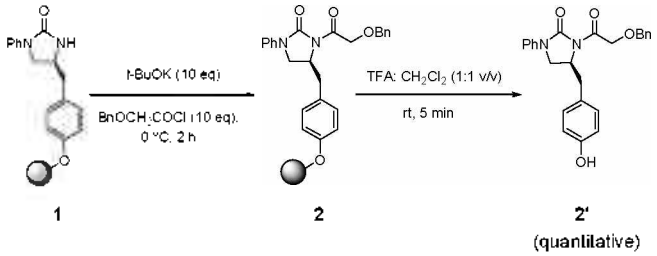
Asymmetric glycolate alkylation reactions in the solid phase were investigated for the first time with good stereoselectivities being obtained by using a Wang resin supported 2-imidazolidinone chiral auxiliary.

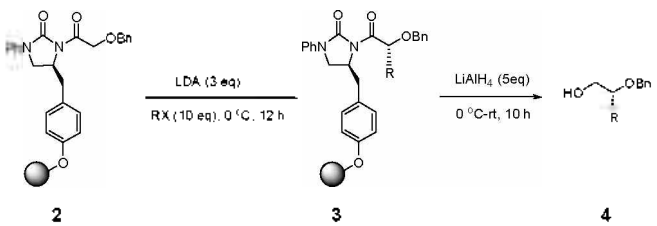
Key Words: Solid phase synthesis, Glycolate alkylation reactions

Introduction

Solid phase synthesis has emerged as a versatile and powerful technique in organic synthesis to prepare chemical libraries, because of its numerous advantages, such as its simple purification process as well as the easy recovery of the expensive reagents.[1] However, stereoselective solid supported chiral auxiliaries still remain a relatively under-developed area.[2] Oxazolidinone chiral auxiliaries are the most extensively explored ones for asymmetric syntheses in the solid phase in many different reactions, such as asymmetric alkylation, aldol condensation, Diels-Alder reactions, and 1,3-dipolar cycloaddition.[3] For the investigation of more powerful solid supported chiral auxiliaries, we previously reported a solid supported 2-imidazolidinone chiral auxiliary, which provided excellent stereoselectivities in asymmetric alkylation reactions.[4] The 2-imidazolidinone chiral auxiliary also exhibited high stereoselectivities in asymmetric glycolate alkylation reactions in the solution phase for the synthesis of chiral benzyl protected α-hydroxy carboxylic acids as important synthetic building blocks.[5] Herein, we wish to report the application of the solid supported 2-imidazolidinone chiral auxiliary to asymmetric glycolate alkylation reactions. To the best of our knowledge, this type of reaction has not been explored in the solid phase so far.



Scheme 1. N-Acylation reaction in the solid phase.



Scheme 2. Asymmetric glycolate alkylation reactions of the Wang resin supported 2-imidazolidinone chiral auxiliary **2**.

Results and Discussion

The solid supported 2-imidazolidinone chiral auxiliary **1** was synthesized according to the previous report[4] with a loading yield of up to 80% on Wang resin (loading capacity 0.87 mmol/g). The N-acylation reaction was carried out by the deprotonation of resin **1** with 10 equiv. of *t*-BuOK in THF, followed by treatment with 10 equiv. of benzyloxyacetyl chloride to afford the acylated resin **2** in quantitative yield (Scheme 1).

Table 1. Stereoselective glycolate benzylations of the Wang resin supported 2-imidazolidinone chiral auxiliary **2**

Entry	Base	Temperature (°C)	Product	Yield (%)[a]	ee (%)[b]
1	NaHMDS	−78°C to −40°C	**4a**	0	-
2	NaHMDS	0 °C	**4a**	10	88
3	LiHMDS	0 °C	**4a**	16	81
4	LDA	0 °C	**4a**	24	90

[a]Yield in four steps based on the original loading of Wang resin. [b]Determined by HPLC (chiracel ODH column).

Table 2. Asymmetric glycolate alkylation reactions of the Wang resin supported 2-imidazolidinone chiral auxiliary **2**

Entry	Alkylating agent RX	Product	Yield (%)[a]	ee (%)[b]
1	BnBr	**4a**	24	90
2	CH_2 = $CHCH_2I$	**4b**	18	89
3	2-Bromomethyl napthalene	**4c**	21	70
4	MeI[c]	**4d**[d]	20[e]	-

[a]Yield in four steps based on the original loading of Wang resin. [b]Determined by HPLC (chiracel ODH column). [c]10% HMPA was added to THF. [d]Inseparable mixture of required product **4d** and unalkylated product (2-benzyloxy ethanol) in 1 : 1 ratio determined by ^{1}H NMR. [e]Yield of inseparable mixture.

Chromatographic TLC monitoring was used to check the progress of the reaction for the cleavage of resin **2** with trifluoroacetic acid (TFA) for 5 min at room temperature.

The N-acylated resin **2** was used to explore the asymmetric glycolate alkylation reactions in the solid phase under several reaction conditions (Scheme 2 and Table 1). The stereoselectivites were examined at the stage of the chiral benzyl-protected α-hydroxy alcohol products, where the enantiomeric excess (ee) values were directly quantified by HPLC using a chiral column.[3a] In the initial experiment, the formation of sodium enolate at −78 °C and its subsequent alkylation with benzyl bromide at the temperature from −78 °C to −40 °C was not successful to afford the product **4a** (Table 1, entry 1). The temperature was an important factor in this case, and by increasing the reaction temperature to 0 °C, product **4a** was obtained in 10% yield (Table 1, entry 2). In addition, replacing sodium enolate with lithium enolate by using LDA or LiHMDS increased the effectiveness of the asymmetric glycolate alkylation reactions, in which LDA was better than LiHMDS in terms of the yield and stereoselectivity (Table 1, entries 3 and 4). A 24% yield of product **4a** with 90% ee was obtained in the benzylation reaction using LDA as a base. The allyl iodide also reacted well to give the products **4b** in 89% ee (Table 2, entry 2). However, lower stereoselectivity (70% ee) was observed in the reaction with 2-bromomethyl naphthalene (Table 2, entry 3). The alkylation with methyl iodide was slow and more difficult as expected due to the lower reactivity of the methyl iodide. Our attempts to conduct the methylation reaction in the solid phase were unsuccessful. The use of HMPA as an additive increased the reactivity, but the reaction still did not go to completion. Therefore, an inseparable mixture of required product **4d** and the unalkylated product (2-benzyloxy ethanol) as a 1 : 1 ratio was obtained after the reductive cleavage of the methylated resin **3d** with $LiAlH_4$ (Table 2, entry 4).

As compared to the same model reactions in the solution phase,[5] the asymmetric glycolate alkylation reactions in the solid phase were more difficult to perform and required a higher temperature. The lithium enolate generated by LDA appeared optimal in most cases of the solid phase reactions. Moreover, the stereoselectivities of the solid phase reactions were somewhat lower than those of the solution phase ones, probably due to the steric hindrance of the microenvironment of the polymeric backbone.

Conclusion

In summary, the Wang resin supported 2-imidazolidinone chiral auxiliary can be used to extend asymmetric glycolate alkylation reactions to the solid phase with good stereoselectivity. The syntheses of chiral benzyl protected α-hydroxy alcohols can be achieved by the reductive cleavage of the alkylated resins with $LiAlH_4$. As compared to the same transformations in the solution phase, the asymmetric glycolate alkylation reactions in the solid phase were more difficult to perform and gave somewhat lower stereoselectivities, probably due to the steric hindrance of the microenvironment of the polymeric backbone.

Experimental Section

Procedure for the preparation of N-acylated resin 2. Resin **1** was swollen in THF under an argon atmosphere at 0 °C. Then, a 1 M solution of *t*-BuOK in THF (10 equiv.) was added dropwise, followed by the addition of benzyloxyacetyl chloride (10 equiv.). The reaction mixture was stirred for 2 h at 0 °C and quenched by adding saturated NH_4Cl solution. The resultant resin **2** was separated from the reaction mixture by filtration, followed by washing with THF/H_2O (1:1 v/v), THF, DMF, CH_2Cl_2, and MeOH sequentially and then dried in vacuo.

To monitor the reaction. Resin **2** was shaken in a 1:1 v/v mixture of dichloromethane and trifluoroacetic acid for 5 min. Then, the resin was filtered and washed with dichloromethane and methanol. The filtrate was concentrated in vacuo to obtain the crude product, which was purified by flash column chromatography to yield compound **2'** as a colorless oil in quantitative yield. ^{1}H NMR ($CDCl_3$) δ 6.6-7.6 (14H, m), 4.79 (2H, d, J = 10.2 Hz), 4.71 (2H, d, J = 1.8 Hz), 4.65 (1H, m), 3.91 (1H, t, J = 9.6 Hz), 3.57 (1H, dd, J = 2.4, 9.6 Hz), 3.24 (1H, dd, J = 3, 13.5 Hz), 2.78 (1H, dd, J = 3, 13.5 Hz).

Typical procedure for the asymmetric glycolate alkylation reactions in the solid phase. Under an Ar atmosphere, resin **2** was swollen in THF and cooled to 0 °C, followed by the dropwise addition of a 2 M solution of LDA in THF (3 equiv.). After continuously stirring for 2 h at the same temperature, the alkyl halide (10 equiv.) was added and reacted for 12 h. Then, the reaction mixture was quenched by adding saturated NH_4Cl solution. The resultant resin **3** was separated from the reaction mixture by filtration, followed by washing with THF : H_2O (1:1 v/v), THF, DMF, CH_2Cl_2, and MeOH sequentially and then dried in vacuo.

Typical procedure for the preparation of chiral benzyl protected α-hydroxy alcohols. Resin **3** was swollen in THF at 0 °C and then a 2 M solution of $LiAlH_4$ in THF (5 equiv.) was added dropwise and reacted at 0 °C for 2 h and at rt for 8 h. The excess of $LiAlH_4$ was quenched with water, 15% aqueous sodium hydroxide, and water in sequence. The reaction mixture was filtered off and washed with methylene chloride. The filtrate was dried over magnesium sulfate and evaporated to obtain the crude product, which was purified by flash column chromatography to yield product **4**.

Compound 4a: Yield 24% in 4 steps based on the original loading of Wang resin; colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.5-7.0 (10H, m), 4.54 (2H, dd, J = 11.2, 21.9 Hz), 3.70 (1H, m), 3.52 (1H, dd, J = 5.6, 11.2 Hz), 2.96 (1H, dd, J = 6.4, 13.7 Hz), 2.81 (1H, dd, J = 6.4, 13.7 Hz); enantiomeric excess 90% determined by HPLC using chiral cell ODH column, eluent *n*-hexane/*i*-PrOH 10:1 v/v, flow rate 0.3 mL/min, detection at 254 nm, retention time 19.6 min (minor) and 21.6 min (major).

Compound 4b: Yield 18% in 4 steps based on the original loading of Wang resin; colorless oil; ^{1}H NMR ($CDCl_3$) δ 7.5-7.0 (5H, m), 5.82 (1H, m), 5.11 (2H, m), 4.69 (1H, d, J = 11.5 Hz), 4.54 (1H, d, J = 11.5 Hz), 3.68 (1H, m), 3.56 (2H, m), 2.37 (2H, m); enantiomeric excess 89% determined by HPLC using chiral cell ODH column, eluent *n*-hexane/*i*-PrOH (10:1 v/v), flow rate 0.5 mL/min, detection at 254 nm, retention time 11.8 min (minor) and 13.9 min (major).

Compound 4c: Yield 21% in 4 steps based on the original loading of Wang resin; colorless oil; ^{1}H NMR ($CDCl_3$) δ 8.0-7.2 (12H, m), 4.55 (2H, dd, J = 11.5, 18.7 Hz), 3.84 (1H, m), 3.72 (1H, m), 3.57 (1H, m), 3.12 (1H, dd, J = 6.4, 13.7 Hz), 2.98 (1H, dd, J = 6.4, 13.7 Hz); enantiomeric excess 70% determined by HPLC using chiral cell ODH column, eluent *n*-hexane/*i*-PrOH 10:1 v/v, flow rate 0.5 mL/min, detection at 254 nm, retention time 19.2 min (minor) and 21.9 min (major).

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References

1. (a) Seneci, P. *Solid Phase and Combinatotial Technologies*; John Willey & Sons: New York, 2000; (b) Obrecht, D.; Villalgordo, J. M. In *Solid-Supported Combinatorial and Parallel Synthesis of Small Molacular-Weight Compound Libraries*; Elsevier Science Ltd: Oxford, 1998. (c) Dolle, R. E.; Nelson, K. H. *J. Comb. Chem.* **1999**, *1*, 235-282.
2. Chung, C. W. Y.; Toy, P. H. *Tetrahedron: Asymmetry* **2004**, *15*, 387-399.
3. (a) Burgess, K.; Lim, D. *Chem. Commun.* **1997**, 785-786; (b) Kotake, T.; Hayashi, Y.; Rajesh, S.; Mukai, Y.; Takiguchi, Y.; Kimuara, T.; Kiso, Y. *Tetrahedron* **2005**, *61*, 3819-3833; (c) Purandare, A. V.; Natarajan, S. *Tetrahedron Lett.* **1997**, *38*, 8777-8780; (d) Phoon, C. W.; Abell, C. *Tetrahedron Lett.* **1998**, *39*, 2655-2658; (e) Winker, J. D.; McCoull, W. *Tetrahedron Lett.* **1998**, *39*, 4935-4936; (f) Faita, G.; Paio, A.; Quadrelli, P.; Rancati, F.; Seneci, P. *Tetrahedron* **2001**, *57*, 8313-8322.
4. Nguyen, Q. P. B.; Kim, J. N.; Kim, T. H. *Tetrahedron Lett.* **2009**, *50*, 4015-4018.
5. Chun, C. C.; Lee, G.-J.; Kim, J. N.; Kim, T. H. *Tetrahedron: Asymmetry* **2005**, *16*, 2989-2992.