Unusual migrations and cyclization in the preparation of \( \beta \)-azido alcohols from \( \beta \)-hydroxy esters†

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Migration of TBDMS and Boc groups from \( 2^\beta \) alcohols to \( 1^\beta \) alcohols during the reduction of \( \beta \)-hydroxy esters has been observed. Also, unusual cyclization has been noticed during tosylation of benzylic alcohol in \( \text{tert}-\text{butyl} \) ((2R)-2-hydroxy-2-phenyl ethyl)carbonate with \( \text{Sn}_2 \) inversion.

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\( \beta \)-Azido alcohols are an important class of compounds, particularly for producing \( \beta \)-amino alcohols by reduction of azide and \( N \)-substituted \( \beta \)-amino alcohols via reductive transformations. These conversions have been usually encountered during many biologically important molecules. Azido alcohols are also good precursors for aziridines and 2-oxazolidinones. Recently, we developed a one-pot conversion of azido alcohols to 2-oxazolidinones using \( \text{PPh}_3 \) in mild carbon dioxide pressure. In this, we needed various azido alcohols. Usually the azido alcohols are prepared by nucleophilic substitution of corresponding halides, sulfonates or oxiranes, aziridines and cyclic sulfates with azide anion. We observed unusual migrations and cyclizations during the preparation of required azido alcohols from readily available \( \beta \)-hydroxy esters. Earlier, we have reported migration of carbonate group during the azide reduction of \( \beta \)-azido carbonates.

Results and Discussion

For the preparation of target azidoalcohol, (2R)-2-azido-3-(4-methoxyphenyl)-propan-1-ol 1, we used the corresponding TBDMS protected hydroxy ester 2. Ester 2 was used earlier in Raggaglitazone. Compound 2 was methylated on phenolic hydroxy group using dimethyl sulfate in the presence of \( K_2\text{CO}_3 \) in acetone. The obtained compound 3 was purified by flash column chromatography and TBDMS group was deprotected with aq. HCl in MeOH at RT to afford the hydroxy ester 4 as a pure solid. Tosylation of 2\( ^\alpha \) hydroxy group of 4 was carried out using TsCl/Et3N in DCM in the presence of DMAP catalyst at RT to give the tosylated product 5. The ester 5 was reduced with NaBH₄ in EtOH at RT to obtain the alcoholic compound 6, which was further reacted with NaN₃ in DMF solvent using TEBA as PTC catalyst to afford the required azido alcohol 1. To prepare 1\( ^\beta \) azido alcohol, which is a positional isomer of 1, compound 3 was reduced with NaBH₄ to yield an unexpected 2\( ^\beta \) aziridinalcohol 7, instead of 7\( ^\alpha \), due to migration of TBDMS group from 2\( ^\alpha \)-OH to 1\( ^\alpha \)-OH. This TBDMS migration was confirmed after obtaining 2\( ^\beta \) azido alcohol 1. Compound 7 was tosyalted and TBDMS group was deprotected by treating it with aqueous HCl to get the compound, which matched with 6. The \( ^1\text{H} \) NMR spectra of compound 6 showed significant change in chemical shift of methyne proton towards downfield (\( \delta \) 4.65) with respect to compound 7 (\( \delta \) 3.9). It confirmed that 2\( ^\alpha \) alcohol in compound 7 was tosyalted, thereby indicating the migration of TBDMS group from 2\( ^\alpha \) to 1\( ^\beta \) alcohol in the reduction of 3. Azidolysis of compound 6 gave 1. The whole sequence is shown in Scheme I.

L-Methyl mandalate 9 (prepared from L-mandalic acid) was treated with (Boc)₂O in DCM in the presence of catalytic amount of DMAP at RT to give 10 in almost quantitative yield. The reaction of 10 with NaBH₄ in ethanol at RT gave a crude compound, which contained a mixture of three compounds on TLC. These three compounds were separated by flash chromatography. The three compounds were characterized as expected compound 12, Boc migrated compound 13 and Boc deprotected compound 11. The compound 12 was tosyalted using TsCl/Et₃N in DCM, and the resulted compound was treated with trifluoroacetic acid (TFA) in DCM at RT to give 14 as a white solid. For the displacement of
tosyl group with azide in the tosyl compound 14, it was reacted in dry conditions with NaN₃ in DMF at 50 °C overnight to afford a crude compound, which was purified by flash chromatography to obtain a pure azido alcohol 8.

The compound 13 was treated with TsCl in DCM in the presence of Et₃N and the resulted compound was treated with TFA in DCM, but there was no change on TLC even after treating with TFA. The solid obtained after processing was characterized as unexpected compound 15 by its analytical and spectral data. For further confirmation, the 13 was treated with TsCl in DCM in the presence of Et₃N to obtain 15 directly. The above reactions are summarized in Scheme II. It can be concluded that the obtained Boc migrated product 13 unusually cyclised while tosylating, to give cyclic carbonate 15. This might be due to nucleophilic attack of carbamidic moiety onto the tosyl bearing center leading to SN₂ cyclization and formation of the inverted product as shown in Scheme III. The sign of specific rotation [α]D²⁵ −26 (c = 1, CHCl₃) of 15 supports the inversion due to SN₂ cyclisation. Similarly, the SN₂ cyclisation was also observed earlier in 2-oxazolidinone chemistry. This cyclization didn’t occur in the case of 12 even though the same tosylation reaction was carried out. It indicates that the non-benzylic tosyl group may be difficult to displace by carbonate nucleophile.

In conclusion, the observations of unusual migrations or cyclizations may find some utility and importance somewhere in organic syntheses.

Experimental Section

Melting points were determined on Buchi 535 melting point apparatus and are uncorrected. IR spectra were recorded in KBr/CHCl₃ on a Perkin-Elmer 1650 Spectrometer; ¹H NMR in CDCl₃ using 200 MHz Varian Gemini spectrometer (chemical shifts in δ, ppm) with TMS as internal standard; and mass spectra on a HP-5989A spectrometer.

Scheme I

Scheme II

Scheme III
Analytical Research Department of Dr. Reddy’s Research Foundation carried out all analytical work. All the organic extracts were dried over sodium sulfate after work-up.

The dry reactions were carried out under nitrogen with magnetic/mechanical stirring. Unless otherwise mentioned all the solvents and reagents used were of LR grade. TLC was performed on precoated silica-gel plates, which were visualized using UV light and sulphuric acid/ethanol (5:95) charring. Flash column chromatography was carried out on silica gel (230-400 mesh) unless otherwise stated.

**Preparation of 3 from 2.** A mixture of 2 (50 g, 0.161 mole), K$_2$CO$_3$ (55.72 g, 0.403 mole) and DMS (22.37 g, 0.177 mole) in acetone (150 mL) was stirred at RT overnight. K$_2$CO$_3$ was removed from reaction mixture by vacuum filtration and it was rinsed thoroughly with acetone (100 mL). The filtrate was concentrated to get crude compound, which was purified by flash chromatography to get 3 as a viscous liquid, yield 83 %; IR (KBr): 2935, 1732 cm$^{-1}$; H NMR (CDCl$_3$): δ 0.0 (s, 3H, -Si-CH$_3$), 0.1 (s, 3H, -Si-CH$_3$), 1.0 (s, 9H, t-Bu), 3.0-3.25 (2dd, 2H, PhCH$_2$-), 3.9 (s, 3H, -OCH$_3$), 4.0 (s, 3H, -OCH$_3$), 4.5 (m, 1H, -CH$_2$-CH-), 7.0 (d, 2H, Ar-H), 7.35 (d, 2H, Ar-H); Mass (m/z): (M$^+$+1) 325.

**Preparation of 4 from 3.** To a cold solution of 3 (9.0 g, 0.027 mole) in methanol (45 mL), aq. HCl (36 wt%, 9 mL) was added. The reaction mixture was stirred at RT for 1 hr. The solution was concentrated in vacuum and ethyl acetate (100 mL) was added. It was washed with water (2 x 25 mL) and concentrated and further washed with pet. ether (50 mL) to get 4 as a white solid, yield 89 %, m.p. 56-58 °C; IR (KBr):
Preparation of tosyl compound 5 from alcohol 4.

**General procedure.** To a cooled solution of ester (5 or 3) (0.00274 mole) in ethanol (5 mL), NaBH₄ (0.00329 mole) was added portionwise and the reaction mixture was stirred for 2 hr at RT. The excess reducing agent was destroyed by addition of saturated NH₄Cl (2 mL) and ethanol was evaporated. The residue obtained was dissolved in ethyl acetate (30 mL), washed with water (2 × 10 mL) and evaporated to obtain alcohols 6 or 7, respectively.

**Compound 6:** Yield 71.8 %, m.p. 131-33 °C; IR (KBr): 3461, 2946, 1511, 1355, 1172 cm⁻¹; ¹H NMR (CDCl₃): δ 2.05 (s, 1H, -OH, D₂O exchangeable), 2.45 (s, 3H, PhCH₂), 2.85 (m, 2H, PhCH₂), 3.7 (m, 2H, -CH₂OH), 3.8 (s, 3H, -OCH₃), 4.65 (m, 1H, -CH₂CH₂-), 6.75, 6.95, 7.25, 7.65 (4d, 8H, Ar-H); Mass (m/z): (M⁺+1) 337.

**Compound 7:** Yield 89.7 %, viscous liquid; IR (KBr): 3468, 2954, 2930, 1613, 1513 cm⁻¹; ¹H NMR (CDCl₃): δ 0.1 (s, 3H, -Si-CH₃), 0.15 (s, 3H, -Si-CH₃), 0.09, 1.0 (2s, 9H, t-Bu), 2.45 (d, 1H, -OH, D₂O exchangeable), 2.8 (t, 2H, PhCH₂), 3.5-3.7 (m, 2H, -CH₃O—), 3.85 (s, 3H, -OCH₃), 3.9 (m, 1H, -CH₂CH₂-), 6.85-7.25 (m, 4H, Ar-H); Mass (m/z): (M⁺+1) 297.

Preparation of azido compounds 1 and 8 from tosyl compounds 6 and 14. General procedure. To a solution of tosyl compound 6 or 14 (0.0059 mole) in DMF (10 mL), NaN₃ (1.93 g, 0.029 mole) and catalytic amount of benzyltributylammonium chloride were added. After stirring the reaction mixture at 80°C for 3 hr, it was poured into iced water and extracted with ethyl acetate. The combined extract was washed with water and concentrated to get azido compounds 1 or 8, respectively.

**Compound 1:** Yield 88.8 %, viscous liquid; IR (KBr): 3421, 2935, 2123, 2108, 1514 cm⁻¹; ¹H NMR (CDCl₃): δ 1.85 (s, 1H, -OH, D₂O exchangeable), 2.8 (d, 2H, -CH₂OH), 3.5-3.8 (m, 3H, PhCH₂ and -CH₂CH₂-), 3.8 (s, 3H, -OCH₃), 6.85 (d, 2H, Ar-H), 7.15 (d, 2H, Ar-H); Mass (m/z): (M⁺+1) 207.

**Compound 8:** Yield 78 %, viscous liquid; IR (KBr): 3400, 2923, 2107, 1707 cm⁻¹; ¹H NMR (CDCl₃): δ 2.4 (d, 1H, -OH, D₂O exchangeable), 3.45 (m, 2H, -CH₂N⁻), 4.9 (m, 1H, -CH₂CH₂-), 7.35 (m, 5H, Ar-H).

Preparation of 6 from 7. To a mixture of alcohol 7 (4.0 g, 0.0135 mole), triethylamine (2.05 g, 0.0203 mole) and catalytic amount of dimethylaminopyridine (DMAP) in DCM (40 mL), tosylchloride (2.92 g, 0.0148 mole) was added portionwise and the reaction mixture was stirred at RT overnight. The reaction mixture was concentrated and the residue was taken in methanol (50 mL) for desilylation. Conc. HCl (5 mL) was then added and stirred for 1 hr. The reaction mixture was concentrated again and the residue obtained was taken in ethyl acetate (100 mL). It was washed with water (2 × 25 mL) and concentrated to get syrupy liquid, which was triturated in IPA (30 mL) to afford 6 as a solid, yield 65 %, m.p. 131-33°C.

Preparation of 11, 12, 13 from 10. To a cooled solution of 10 (10 g, 0.0375 mole) in ethanol (50 mL), NaBH₄ (2.13 g, 0.0563 mole) was added portionwise and the reaction mixture was stirred for 2 hr at RT. The excess reducing agent was destroyed by addition of saturated NH₄Cl (10 mL) and ethanol was evaporated. The residue obtained was dissolved in ethyl acetate (200 mL), washed with water (3 × 50 mL) and evaporated to obtain crude mixture. This was subjected to flash column chromatography to separate three compounds 11, 12 and 13.

**Compound 11:** Yield 3 %, m.p. 52-54 °C; IR (KBr): 3374 cm⁻¹; ¹H NMR (CDCl₃): δ 12.9 (bs, 2H, 2-OH), 3.55-3.8 (m, 2H, -CH₂O—), 4.8 (m, 1H, -CH₂CH₂-), 7.3 (m, 5H, Ar-H); Mass (m/z): (M⁺+1) 121 (-OH).

**Compound 12:** Yield 40 %, viscous liquid; IR (KBr): 3454, 2983, 1821, 1747 cm⁻¹; ¹H NMR (CDCl₃): δ 1.45 (s, 9H, t-Bu), 3.7-4.0 (m, 2H, -CH₂OH), 5.6 (m, 1H, -CH₂CH₂-), 7.3-7.5 (m, 5H, Ar-H).
Compound 13: Yield 40%, viscous liquid; IR (KBr): 3437, 2982, 1743 cm⁻¹; ¹H NMR (CDCl₃): δ 1.5 (s, 9H, t-Bu), 2.65 (s, 1H, -OH, D₂O exchangeable), 4.05-4.3 (m, 2H, -CH₂₂ -), -CHCH (KBr): 3437, 2982, 1743 cm⁻¹; 'H NMR

Preparation of 14 from 12. To a mixture of 12 (5.0 g, 0.021 mole), triethylamine (3.2 g, 0.0315 mole) and catalytic amount of DMAP in DCM (50 mL), tosyl chloride (4.4 g, 0.0231 mole) was added and the reaction mixture was stirred at RT overnight. The reaction mixture was washed with water (2 x 10 mL) and concentrated to get a residue. This was taken into DCM (50 mL), followed by the addition of trifluoroacetic acid (TFA) (5 mL) and concentrated to get a residue. This residue was purified from pet. ether (30 mL) to obtain 14 as a white solid, yield 64.2%, m.p. 57-59°C; IR (KBr): 3539, 1813 cm⁻¹; ¹H NMR (CDCl₃): δ 2.4 (s, 3H, PhCH₃), 2.65 (s, 1H, -OH, D₂O exchangeable), 3.95-4.2 (m 2H, -CH₂₂ -), 4.95 (d, 1H, -CHCH₂ -), 7.25-7.45 (m, 7H, Ar-H), 7.75 (d, 2H, Ar-H); Mass (m/z): (M⁺+1) 275

Preparation of 15 from 13. To a mixture of 13 (5.0 g, 0.021 mole), triethylamine (3.2 g, 0.0315 mole) and catalytic amount of dimethylanilopyridine (DMAP) in DCM (50 mL), tosyl chloride (4.4 g, 0.0231 mole) was added and the reaction mixture was stirred at RT overnight. The reaction mixture was washed with water (2 x 10 mL) and concentrated to get solid, which was purified by trituration with pet. ether (30 mL) to obtain 15 as an unexpected compound, yield 67.5%, m.p. 79-81°C; IR (KBr): 3437, 2982, 1743 cm⁻¹; ¹H NMR (CDCl₃): δ 1.5 (s, 9H, t-Bu), 2.65 (s, 1H, -OH, D₂O exchangeable), 4.05-4.3 (m, 2H, -CH₂₂ -), -CHCH (KBr): 3437, 2982, 1743 cm⁻¹; 'H NMR

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