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Unexpected Formation of Azetidines Through Staudinger Reaction of 3-Azido-1,2-diols

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ABSTRACT

A mechanistic study of Staudinger reaction of 3-azido-1,2-diols has led to the formation of both azetidines and aziridines depending on experimental conditions. The separation of mixture of regioisomers of azido-diol was second order and carried out by tosylation and mesylation of both hydroxyl groups present. The electronic and steric properties of phosphine had no significant impact on the overall selectivity of the reaction but did affect the products yields. Finally, this reaction was carried out in different solvents and the choice of solvent was crucial on the time of reaction, enabling the formation of both functionalized aziridines and azetidines.

KEYWORDS

Staudinger reaction, Aza-Wittig reaction, Aziridine, Azetidine, Azido-alcohol.

INTRODUCTION

Staudinger reaction [1], discovered nearly a century ago, occurs between a phosphine and an azide to form an aza-ylide. This transformation has been exploited in several reactions of high synthetic importance, wherein aza-ylide intermediate serves to trap various electrophiles [2]. This reaction was also used to get an insight on complex biological systems [3,4] and was considered as a new possibility for probing intercellular interactions [3]. Therefore, it has been recognized as a useful reaction in organic chemistry and biology [5-10]. The growing importance of azido-alcohols as intermediates toward the synthesis of aziridines [11] and amino alcohols [12] in organic synthesis and their presence in bioactive molecules, has kept on the need for developing them.

Over the past several years, important advances have been made toward these targeted intermediates. Generally, they were synthesized by reduction of azido ketones [13], conversion of diols *via* cyclic sulfates or sulfites [14] and asymmetric ring-opening of oxiranes by the azide anion [15]. During our investigations, we became interested in the synthesis of 3-azido-2-hydroxypropyl-4methylbenzosulfonate **3a** by ring-opening of epoxides with azide nucleophiles, according to literature [16,17].

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Thus aziridines are versatile synthetic intermediates for the preparation of a variety of aliphatic and ring-expanded amines through their regio- and stereoselective ring-opening with various nucleophiles [11]. The higher homologues of aziridines, have acquired a prominent position in organic chemistry as well. Along with their synthetic relevance [12,13a], compounds containing an azetidine moiety have been shown to possess a wide range of biological activities [14a]. In particular, 3-alkoxy- and 3-aryloxyazetidines have been described with a number of activities such as G-protein-coupled receptor agonists [18], inhibitors of stearoyl-coenzyme d-9 desaturase [5b] and antibacterial agents [6c].

Needless to say that many azido-alcohols served to prepare aziridines starting from *o*-protected glycidol and its derivatives [19-22]. Other conversions dealt with allylic alcohols that were transformed into aldehydes and further used for chain homologation by means of Wittig reaction [23].

Herein, we report our findings on the preparation of useful azido-diols through the reaction of sodium azide with oxiran-2-ylmethylbenzensulfonate. The reaction afforded functionalized aziridines and azetidines bearing hydroxyl, tosyl, mesyl or ditosyl groups. The reactivity of mixture of two azides was investigated in the presence of triphenylphosphine (PPh_3) and tributylphosphine (PBu_3). Needless to say that no investigation was found on the reactivity of either both free-diols or their protected counterparts when reacted with phosphines. Moreover, no attention had been directed to fundamental mechanistic studies that would allow optimization of rates and yields of reaction. The influence of temperatures and the choice of solvents have also been discussed.

EXPERIMENTAL

All the reactions were performed under anhydrous conditions using dry solvents and carried out under nitrogen atmosphere. Solvents were purified and dried according to standard procedures. Reagents for synthesis were used as commercially received. Infrared spectra were recorded using a Mattson Genesis II FTIR instruments. NMR spectra were recorded at 25 °C in $CDCl_3$ (0.004 mmol L^{-1}) on a Bruker 500, or 300 MHz instrument, using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ (ppm) and coupling constant (*J*) values in Hertz (Hz). ESI-MS data were recorded in the positive ion mode on a quadrupole instrument (Waters-Micromass ZQ). Column chromatography was performed on silica gel 230-270 mesh (Merck) using CH_2Cl_2, MeOH or mixture of both according to thin layer chromatography assays.

Oxiran-2-ylmethyl 4-methylbenzenesulfonate (2): Dry triethylamine (10.9 g, 10.81mmol) and *p*-toluenesulfonyl chloride (20.61 g, 11 mmol) were added to a stirred solution of (±)-glycidol (2 g, 27.02 mmol) in dry CH_2Cl_2, under nitrogen atmosphere at 0 °C. The reaction mixture was stirred at room temperature overnight. After reaction completion, the resulting mixture was diluted with CH_2Cl_2 and washed once with an aqueous solution of NH_4Cl. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The glycidol tosylate was obtained as a pasty mass in a good yield (81.2 %). IR (KBr, ν_{max}, cm^{-1}): 1366.22 (S=O), 1176.69 (C–O), 915.22 (S–O), 687.75-665.05 (OTs). ^{1}H NMR δ $CDCl_3$ 300 MHz: 2.41 (s, C**H$_3$**), 2.55 (d, 2H, *J* = 13.8 Hz, C**H$_2$**), 2.75 (m, 1H, C**H**), 3.89 (dd, 1H, *J* = 6.3 Hz, *J* = 5.1 Hz, C**H$_2$**OTs), 4.2 (dd, 1H, *J* = 6.3 Hz, *J* = 5.1 Hz, C**H$_2$**OTs), 7.3 (d, 2H, *J* = 8 Hz, **Ar**), 7.70 (d, 2H, *J* = 8 Hz, **Ar**). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 144.39, 139.98, 130.49, 128.20, 50.66, 43.89, 21.29. (MS-ESI): *m/z* measured at 250.8 for [M^+Na^+], calculated at 251 for $C_{10}H_{12}O_4SNa$.

3-Azido-2-hydroxypropyl-4-methylbenzosulfonate (3a) and 2-azido-3-hydroxypropyl-4-methylbenzosulfonate (3b): A solution of (±)-glycidol (2 g, 8.8 mmol) in ethanol (50 mL) was treated with ammonium chloride (0.5 g, 9.61 mmol) and sodium azide (0.62 g, 9.62 mmol). The resulting mixture was slowly warmed to reflux for 1.5 h and heated at 70-75 °C for 50 min. The solution was allowed to cool to room temperature. The reaction mixture was filtered and the solid residue was washed with ethanol several times. The residue was dissolved in ether (200 mL) and washed with water and the aqueous layer was extracted with ether. The combined organic layers were dried over magnesium sulfate and concentrated to yield a mixture of azides **3a** and **3b** as yellow viscous oil (1:0.3). The latter was used without further purification, because chromatographic separation was not possible at this stage. The ratio of **3a/3b** was determined by ^{1}H NMR.

3-Azido-2-hydroxypropyl-4-methylbenzosulfonate (3a): IR (KBr, ν_{max}, cm^{-1}): 3387.31 (O–H), 1356.78 (S=O), 1177.09 (C–O), 932.53 (S–O), 714.5-667.07 (OTs). ^{1}H NMR δ $CDCl_3$: 500 MHz: 2.36 (s, 3H, CH_3), 3.28 (dd, 1H, *J* = 4.8 Hz, *J* = 9.2 Hz, **H**HCN_3), 3.29 (m, 1H, **H**COH), 3.31 (dd, 1H, *J* = 4.8 Hz, *J* = 9.2 Hz, **H**HCN_3), 3.48 (s broad, OH), 3.94 (dd, 1H, *J* = 5 Hz, *J* = 10 Hz, C**H**HOTs), 3.96 (dd, 1H, *J* = 5 Hz, *J* = 10 Hz, C**H**HOTs), 7.30 (d, 2H, *J* = 6.2 Hz, Ar), 7.73 (d, 2H, *J* = 6.2 Hz, Ar). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.18, 131.65, 129.73, 127.54, 70.41, 67.93, 53.44, 21.17. (MS-ESI): *m/z* measured at 293.9 for [M+Na^+], calculated at 294 for $C_{10}H_{13}N_3O_4SNa$.

2-Azido-3-hydroxypropyl-4-methylbenzosul-fonate (3b): IR (KBr, ν_{max}, cm^{-1}): 3387.31 (O–H), 1356.78 (S=O), 1177.09 (C–O), 932.53 (S–O), 714.5-667.07 (OTs). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.36 (S, 3H, CH_3), 3.38 (m, 1H, **H**CN_3), 3.84 (dd, 1H, *J* = 4.7z, *J* = 9.2 Hz, **H**HCOH), 3.86 (dd, 1H, *J* = 4.1 Hz, *J* = 9.2 Hz, **H**HCOH), 3.48 (s broad, OH), 3.90 (dd, 1H, *J* = 4.8 Hz, *J* = 11.4 Hz, C**H**HOTs), 3.96 (dd, 1H, *J* = 5.7 Hz, *J* = 11.4 Hz, C**H**HOTs), 7.30 (d, 2H, *J* = 6.2 Hz, Ar), 7.73 (d, 2H, *J* = 6.2 Hz, Ar). ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.18, 131.65, 129.73, 127.54, 70.41, 69.26, 52.27, 21.17; (MS-ESI): *m/z* measured at 293.9 for [M+Na^+], calculated at 294 for $C_{10}H_{13}N_3O_4SNa$.

Reaction of the mixture of 3a and 3b

Aziridin-2-ylmethylbenzensulfonate (6): To a solution of mixture of **3a** and **3b** (1.25g, 4.99 mmol) in acetonitrile (50 mL), triphenylphosphine (PPh_3, 1.33 g, 5.06 mmol) were added and the reaction mixture was stirred at room temperature until the evolution of nitrogen ended (45 min) and then the mixture was gently refluxed for 3 h. After cooling, the solvent was removed on a rotary evaporator and the residue was repeatedly extracted with boiling petroleum ether (b.p. 40-60 °C). Removal of solvent afforded an oily residue consisting of a mixture of aziridinetosylate (**6**), azetidinemethanol (**7a**) and aziridine-

methanol (**7b**) along with triphenylphosphine oxide. Removal of the latters (**7a** and **7b**) performed first by dissolving the mixture in anhydrous ether (30 mL) and cooled at 0 °C. Then purification was performed by column chromatography using a mixture of CH_2Cl_2/CH_3OH (1:1) as eluent. Pure aziridine-tosylate (**6**) was obtained as yellow oil (71 %).

R_f = 0.94, IR (KBr, ν_{max}, cm^{-1}): 3362.53 (N–H), 1363.15 (S=O), 1119.20 (C–O), 931.10 (S–O), 722.28-696.32 (OTs). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (s, N**H**), 1.36 (dd, *J* = 5 Hz, *J* = 10 Hz, C**H**$_2$), 1.79-1.83 (m, C**H**), 1.82 (dd, 2H, *J* = 5 Hz, *J* = 10 Hz, C**H**$_2$), 2.35 (s, C**H**$_3$), 3.26 (dd, 1H, *J* = 5 Hz, *J* = 10 Hz, C**H**$_2$OTs,), 3.48 (dd, 1H, *J* = 5 Hz, *J* = 10 Hz, C**H**$_2$OTs), 7.67 (d, 2H, *J* = 5 Hz, C**H**$_2$OTs), 7.48 (d, 2H, *J* = 5 Hz, C**H**$_2$OTs). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 144.39, 140.29, 130.48, 128.27, 76.28, 29.79, 22.68, 21.29. (MS-ESI): *m/z* measured at 249.8 for [M+H$^+$], calculated at 250 for $C_{10}H_{13}NO_3SH$.

Azetidin-3-ol (7a): R_f = 0.53, IR (KBr, ν_{max}, cm^{-1}): 3362.53 (N–H), 1363.15 (S=O), 1119.20 (C–O), 931.10 (S–O), 722.28-696.32 (OTs). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.44 (s, N**H**), 3.92 (dd, 1H, *J* = 5 Hz, *J* = 10 Hz, C**H**$_2$NH), 3.98 (dd, 1H, *J* = 5 Hz, *J* = 10 Hz, C**H**$_2$NH), 4.09 (m, C**H**OH), 4.55 (s, O**H**). ^{13}C NMR (75.4 MHz, $CDCl_3$) 56.52, 63.56. (MS-ESI): *m/z* measured at 74.3 for [M+H$^+$], calculated at 74 for C_3H_7NOH.

Aziridin-2-ylmethanol (7b): R_f = 0.73, IR (KBr, ν_{max}, cm^{-1}): 3362.53 (N–H), 1363.15 (S=O), 1119.20 (C–O), 931.10 (S–O), 722.28-696.32 (OTs). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.24 (s, N**H**), 1.32 (dd, 1H, *J* = 5 Hz, *J* = 10 Hz, C**H**$_2$), 1.60-1.64 (m, C**H**), 1.79 (dd, 1H *J* = 5 Hz, *J* = 10 Hz, C**H**$_2$), 3.10 (dd, 1H, *J* = 5 Hz, *J* = 10 Hz, C**H**$_2$OH), 3.22 (dd, 1H, *J* = 5 Hz, *J* = 10 Hz, C**H**$_2$OH), 4.16 (s, O**H**). ^{13}C NMR (75.4 MHz, $CDCl_3$) δ: 72.3, 32.6, 22.68. (MS-ESI): *m/z* measured at 74.1 for [M$^+$H$^+$], calcu-lated at 74 for $C_4H_{11}NOH$.

Separation of mixture of 3a and 3b

Tosylation of mixture of 3a and 3b: Dry triethylamine (TEA) (0.26 g, 2.6 mmol) and *p*-toluenesulfonyl chloride (0.3 g, 1.7 mmol) were added to a stirred solution of mixture of azido-alcohols **3a** and **3b** (0.23 g, 0.86 mmol) in dry CH_2Cl_2, under nitrogen at 0 °C. The reaction mixture was stirred at room temperature for 18 h. After the reaction completion, the resulting mixture was diluted with CH_2Cl_2 and washed once with an aqueous solution of NH_4Cl. The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude product was obtained as a pasty mass in a good yield (90 %). The crude product (0.20 g) was subjected to preparative thin layer chromatography (TLC) using a mixture of CH_2Cl_2/CH_3OH (9:1) as eluent. The pure azido-alcohol **8a** was obtained in a moderated yield (65 %).

3-Azidopropane-1,2-diyl bis(4-methylbenzensulfonate) (8a): R_f = 0.87, IR (KBr, ν_{max}, cm^{-1}): 2103.38 (N_3), 1364.63 (S=O), 1172.67 (C–O), 911.83 (S–O), 687.17-661.00 (OTs). ^{1}H NMR (500 MHz, $CDCl_3$): 2.44 (S, 6H, 2CH_3), 3.38 (dd, 1H, *J* = 5 Hz, *J* = 15 Hz, C**H**HN_3), 3.43 (dd, 1H, *J* = 5 Hz, *J* = 15 Hz, C**H**HN_3), 3.91 (dd, 1H, *J* = 5 Hz, *J* = 15 Hz, C**H**HOTs), 3.99 (dd, 1H, *J* = 5 Hz, *J* = 15 Hz, C**H**HOTs), 4.03-4.06 (m, 1H, **H**COTs), 7.36 (d, 4H, *J* = 5 Hz, 2Ar), 7.79 (d, 4H, *J* = 5 Hz, 2Ar). ^{13}C NMR (126 MHz, $CDCl_3$) δ: 136.27, 132.38, 131.86, 131.78, 129.81, 128.38, 128.29, 67.05, 53.34, 50.18, 21.51. (MS-ESI): *m/z* measured at 447.9 for [M$^+$Na$^+$], calculated at 448 for $C_{17}H_{19}N_3O_6S_2Na$.

Reaction of 8a: A solution of (0.15 g, 0.43 mmol) of **8a** in CH_3CN was cooled at 0 °C. Triphenylphosphine (0.11 g, 0.43 mmol) was added over a period of 0.5 h in five portions. The solution was stirred at room temperature for 1.5 h and then heated at 80 °C for another 6 h. Dimethyl formamide was removed *in vacuo* and the resulting residue was purified by column chromatography on silica gel with a mixture of diethyl ether and petroleum ether 40-60 (1:3) affording azirdine-tosylate (**6**) and azetidintosylate (**11**).

Azetidin-3-yl-4-methylbenzensulfonate (11): R_f = 0.90, IR (KBr, ν_{max}, cm^{-1}): 3362.53 (N–H), 1363.15 (S=O), 1119.20 (C–O), 935.52 (S–O), 721.11-699.12 (OTs). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.5 (s, N**H**), 3.81 (dd, 1H, *J* = 3 Hz, *J* = 13.2 Hz, C**H**$_2$NH), 3.52 (dd, 1H, *J* = 3 Hz, *J* = 13.2 Hz, C**H**$_2$NH), 5.49 (m, C**H**OTs), 7.69 (d, 2H, *J* = 8.1 Hz, Ar), 7.37 (d, 2H, *J* = 8.1 Hz, Ar). ^{13}C NMR (75.4 MHz, $CDCl_3$) d: 144.38, 140.29, 131.86, 128.29, 61.91, 50.60, 21.3 (MS-ESI): *m/z* measured at 228.6 for [M$^+$H$^+$], calculated at 228.06 for $C_{10}H_{13}NO_3SH$.

Mesylation of the mixture of 3a and 3b: Dry triethylamine (0.18 g, 1.7 mmol) and methansulfonyl chloride (0.14 g, 1.19 mmol) were added to a stirred solution of mixture of **3a** and **3b** (0.16 g, 0.6 mmmol) in dry CH_2Cl_2, under nitrogen atmosphere at 0 °C. The reaction mixture was stirred at room temperature for 18 h. After the reaction completion, the resulting mixture was filtered and diluted with CH_2Cl_2 and then washed once with an aqueous solution of NH_4Cl. The organic layer was dried over Na_2SO_4 and the solvent was removed under reduced pressure. The crude product was obtained as paste in a good yield (80%). This mass was purified by preparative TLC using a mixture of CH_2Cl_2/CH_3OH (9:1) as eluent. Pure **10a** was obtained in a reasonable yield (65 %).

3-Azido-2-((methylsulfonyl)oxy)propyl-4-methyl-benzensulfonate) (10a): R_f = 0.85, IR (KBr, ν_{max}, cm^{-1}): 2103.95 (N_3), 1364.72 (S=O), 1174.48 (C–O), 912.46 (S–O), 703.03-687.29 (OTs). ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.36 (S, 3H, CH_3), 3.38 (m, 1H, **H**CN_3), 3.84 (dd, 1H, **H**HCOH, *J* = 4.6, *J* = 11.2Hz), 3.86 (dd, 1H, *J* = 4.1 Hz, *J* = 11.2 Hz, **H**HCOH), 3.48 (s broad, OH), 3.94 (dd, 1H, *J* = 4.5 Hz, *J* = 9.8 Hz, C**H**HOTs), 3.96 (dd, 1H, C**H**HOTs, *J* = 4.3 Hz, *J* = 9.8Hz), 7.30 (d, 2H, *J* = 6.9 Hz, Ar), 7.73 (d, 2H, *J* = 6.8 Hz, Ar).^{13}C NMR (126 MHz, $CDCl_3$) δ 145.18, 131.65, 129.73, 127.54, 70.41, 69.26, 52.27, 21.17. (MS-ESI): *m/z* measured at 371.8 for [M$^+$Na$^+$], calculated at 372 for $C_{11}H_{15}N_3O_6S_2Na$.

Reaction of 10a: The same procedure was applied to **10a** for the synthesis of **8a**. Purification was performed first dissolving the reaction mixture in ether (50 mL) and the mixture was cooled to 0 °C. Triphenylphosphine oxide was removed by filtration and the solvent removed and this procedure was repeated twice. The resulting residue was purified by column chromatography using a mixture of CH_2Cl_2/CH_3OH (9:1) as eluent affording azirdinetosylate (**6**) and azetidine mesylate (**14**).

Azetidin-3-yl methanesulfonate (14): R_f = 0.65, IR (KBr, ν_{max}, cm^{-1}): 3350.22 (N–H), 1350.18 (S=O), 1133.20 (C–O), 925.18 (S–O). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.03 (s, NH),

2.89 (s, 3H, CH_3), 3.10 (dd, 1H, J = 3 Hz, J = 13.2 Hz, C**H**HNH), 3.17 (dd, 1H, J = 3 Hz, J = 13.2 Hz, C**H**HNH), 4.04 (m, 1H, CHOMs). ^{13}C NMR (75.4 MHz, $CDCl_3$) d: 63.80, 51.50, 38; (MS-ESI): *m/z* measured at 173.1 for [M^+Na^+], calculated at 174 for $C_4H_9NO_3SNa$.

The same procedure was used for mixtures **3a** and **3b**, **8a** and **10a** (1eq) and with tripbutyphosphine PBu_3 (1 eq) under different conditions affording the same products, mainly consisting of aziridinetosylate (**6**) compound as shown in Tables 1-3.

RESULTS AND DISCUSSION

Staudinger reaction of the mixture of 3-azido-2-hydroxypropyl-4-methyl benzosulfonate (3a) and 2-azido-3-hydroxypropyl-4-methylbenzosulfonate (3b): The first step was the *o*-protection of glycidol **1** with *p*-toluenesulfonyl chloride (TsCl) in the presence of triethylamine and led to the formation of **2** in good yield (80 %) (**Scheme-I**). The ethanolic solution of compound **2** was treated with ammonium chloride and sodium azide to afford an mixture of two regioisomeric azido-diols (**3a** and **3b**). Nucleophilic attack of glycidol was observed to occur exclusively at the secondary C-2 carbon and led predominantly to azide **3a**. Similarly the cleavage of the oxide led azide **3b** as a result of a nucleophilic attack at the tertiary carbon atom (C-1).

TABLE-1
EFFECT SOLVENT ON THE RATE AND YIELD OF STAUDINGER REACTION OF MIXTURE OF AZIDES **3a** AND **3b**

Solvents	Temperature	Time (h)	Phosphines	R (%)
Acetonitrile	Reflux 70 °C	2.5	PBu_3	72
	Reflux 70 °C	3.0	PPh_3	65
THF	Reflux 70 °C	10	PBu_3	67
	Reflux 70 °C	16	PPh_3	51
Toluene	Reflux 90 °C	6.5	PBu_3	59
	Reflux 90 °C	6.0	PPh_3	55
DCM	0 °C → RT	24	PBu_3	69
	0 °C → RT	18	PPh_3	58
Ether	0 °C → RT	48	PBu_3	62
	0 °C → RT	48	PPh_3	60
DMF	0 °C → RT	16	PBu_3	48
	0 °C → RT	12	PPh_3	30
Ether	0 °C → RT	48	PBu_3	62
	0 °C → RT	48	PPh_3	60
DMF	0 °C → RT	16	PBu_3	48
	0 °C → RT	12	PPh_3	30

TABLE-2
EFFECT SOLVENT ON THE RATE AND YIELD OF STAUDINGER REACTION OF AZIDO **8a**

Solvents	Temperature	Time (h)	Phosphines	R (%)
Acetonitrile	Reflux 70 °C	3	PBu_3	82
	Reflux 70 °C	3	PPh_3	70
THF	Reflux 70 °C	16	PBu_3	77
	Reflux 70 °C	18	PPh_3	71
Toluene	Reflux 90 °C	8.0	PBu_3	69
	Reflux 90 °C	8.5	PPh_3	60
DCM	0 °C → RT	24	PBu_3	72
	0 °C → RT	18	PPh_3	68
Ether	0 °C → RT	48	PBu_3	68
	0 °C → RT	48	PPh_3	61
DMF	0 °C → RT	16	PBu_3	45
	0 °C → RT	12	PPh_3	40
THF	Reflux 70 °C	16	PBu_3	77
	Reflux 70 °C	18	PPh_3	71

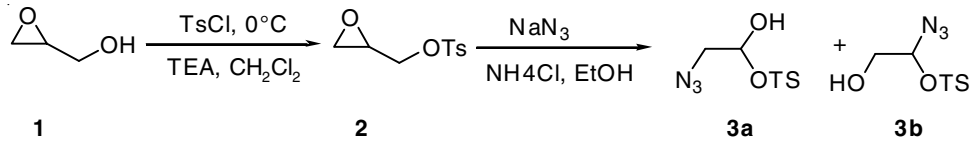
TABLE-3
EFFECT SOLVENT ON THE RATE AND YIELD OF STAUDINGER REACTION OF AZIDE **10a**

Solvents	Temperature	Time (h)	Phosphines	R (%)
Acetonitrile	Reflux 70 °C	3	PBu_3	78
	Reflux 70 °C	3	PPh_3	71
THF	Reflux 70 °C	16	PBu_3	76
	Reflux 70 °C	18	PPh_3	74
Toluene	Reflux 90 °C	8	PBu_3	66
	Reflux 90 °C	8	PPh_3	61
DCM	0 °C → RT	24	PBu_3	70
	0 °C → RT	18	PPh_3	65
Ether	0 °C → RT	48	PBu_3	65
	0 °C → RT	48	PPh_3	62
DMF	0 °C → RT	16	PBu_3	41
	0 °C → RT	12	PPh_3	39
THF	Reflux 70 °C	16	PBu_3	76
	Reflux 70 °C	18	PPh_3	74

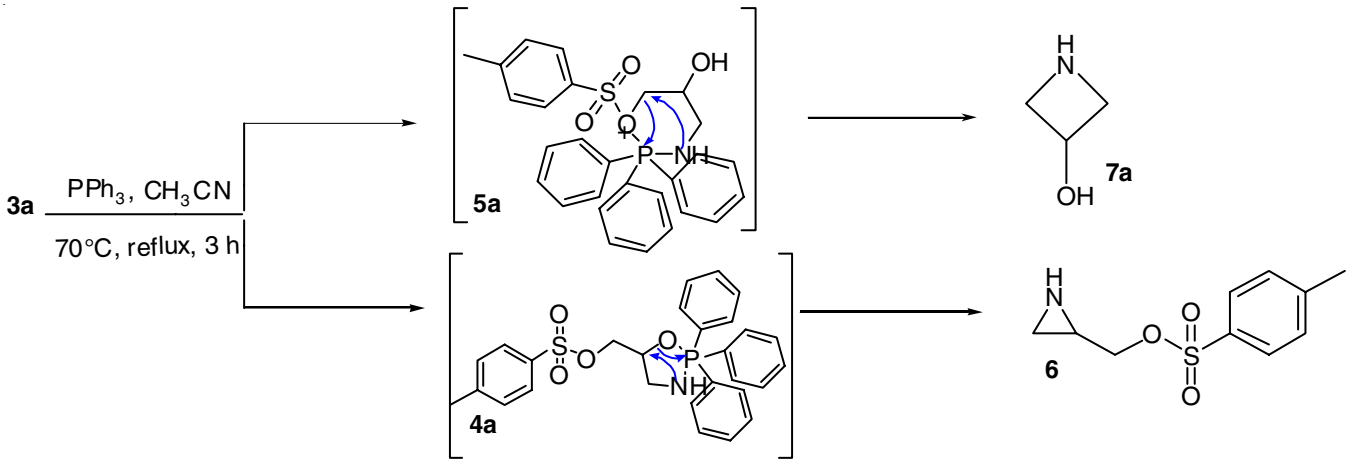
The composition of mixture of **3a** and **3b** was determined by ^{1}H NMR and found to be 1:0.3. The separation could not be carried out by gas chromatography or recrystallization. In the following step, the synthesis of aziridine involved the reaction between **3a** and **3b** with triphenylphosphine. The reaction was monitored by ^{1}H NMR and mass spectroscopy. The reaction was somewhat complex since both azides led to the same aziridinetosylate **6**, as a result of an intramolecular addition reaction generating oxazaphospholidines **4a** and **4b**. Thermal cleavage of P-N bond led to the formation of aziridine-tosylate (**6**), (**Schemes IIa and IIb**).

As far as the reactivity of **3a** was concerned, **7a** was isolated as side product resulting from the oxaphosphane **5a** from the reaction when the oxygen of the tosyl group reacted with the phosphorus atom of triphenylphosphine (**Scheme-IIa**). Aziridinemethanol **7b** was formed as second product from **3b** resulting when the oxygen of the tosyl group was involved in the formation of the oxaphosphane **5b** (**Scheme-IIb**). Staudinger reaction of the mixture of **3a** and **3b** proceeded in 30-72 % yields and afforded mixtures of aziridines and azetidines due to different reactivities of each oxygen present on distinct azide.

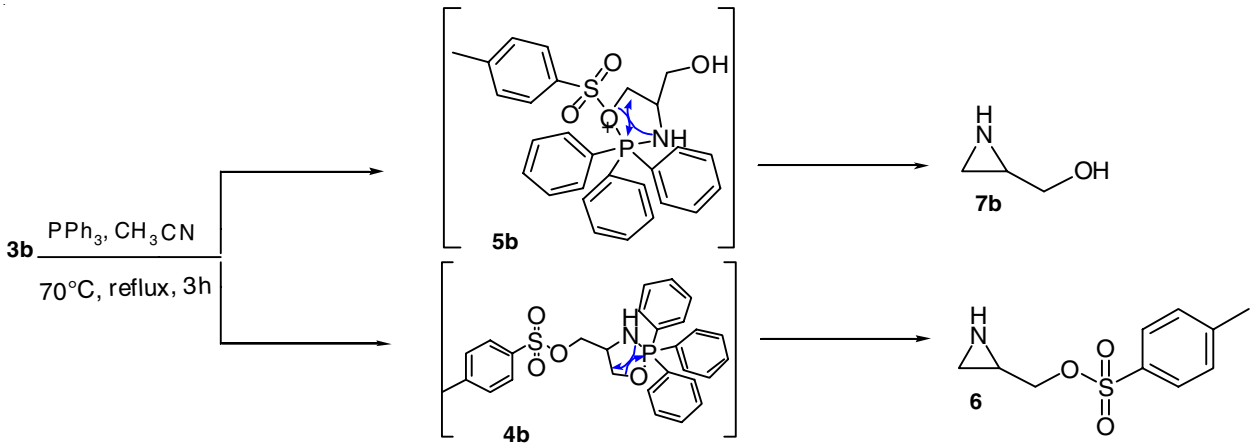
The effect of solvent on the reaction was also examined and the results are shown in Table-1. This reaction proceeded more rapidly in polar, aprotic solvents and the best among them was acetonitrile. Besides, phosphines such as triphenylphosphine and tributylphosphine were used in this investigation. The reaction was completely finished in few hours. When tributylphosphine was used, results were quite different from those obtained with triphenylphosphine. It important to single out that steric hindrance of triphenylphosphine had no effect on the selectivity toward reactivity of both oxygen in both azides **3a** and **3b**, as compared to tributylphosphine.The advantage of the use of tributylphosphine was due to formation of the products with higher yields and removal of tributylphospine oxide was much easier than of triphenylphosphine oxide.



Scheme-I: Synthesis of azido-alcohol



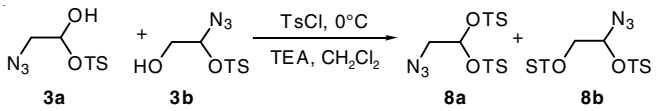
Scheme-IIa: Reaction of 3-azido-2-hydroxypropyl-4-methylbenzo-sulfonate (**3a**)



Scheme-IIb: Reaction of 2-azido-3-hydroxypropyl-4-methylbenzo-sulfonate (**3b**)

Staudinger reaction of the 3-azidopropane-1,2-diyl bis(4-methyl-benzensulfonate) (8a)

Separation of mixture of azides 3a and 3b by tosylation: The separation of mixture of two azides was achieved by tosylation of both **3a** and **3b** in the presence of TsCl and triethylamine (**Scheme-III**). This made the easy separation of regio-isomers 3-azidopropane-1,2-diyl *bis*(4-methylbenzene-sulfonate) **8a** and 2-azidopropane-1,3-diyl *bis*(4-methyl-benzenesulfonate) **8b** by column chromatography, using dichloromethane and methanol (CH_2Cl_2/CH_3OH 9:1) as eluent.



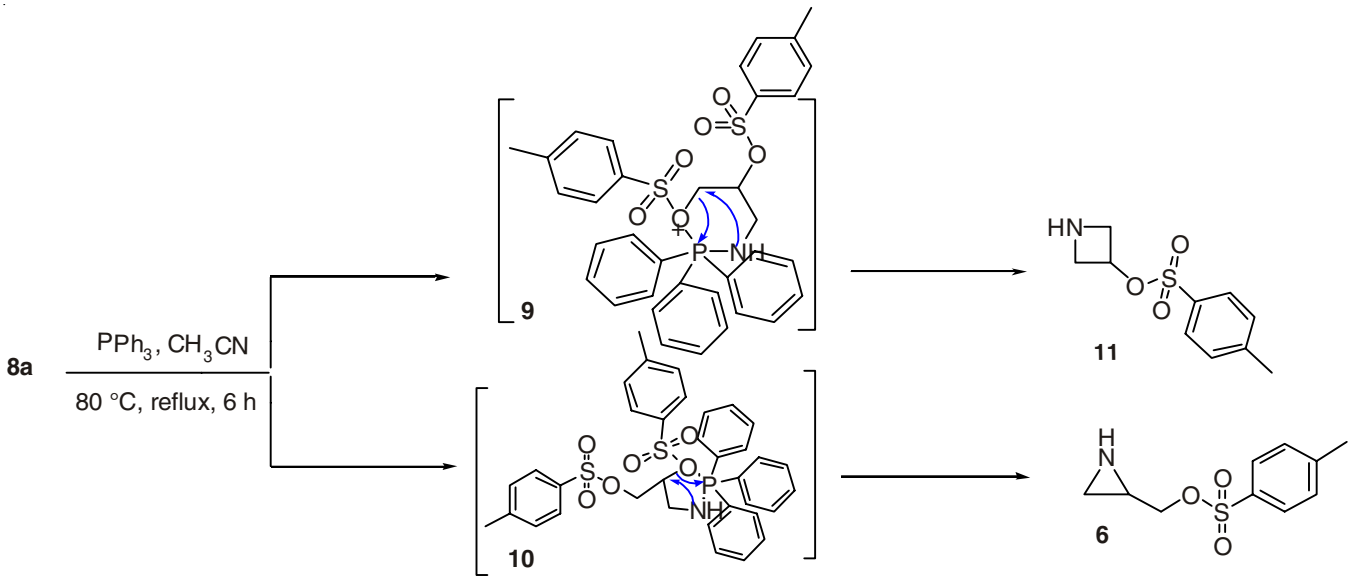
Scheme-III: Tosylation of the mixture of **3a** and **3b**

Azide (**8a**) was readily converted into aziridine tosylate (**6**) by treatment with triphenylphosphine, processing through the intermediate oxaphospholidine (**10**). The reaction furnished azetidintosylate (**11**) as minor product (**Scheme-IV**). The result observed might be a consequence of difference in reactivity between both oxygen atoms and phosphines that induced an efficient kinetic resolution.

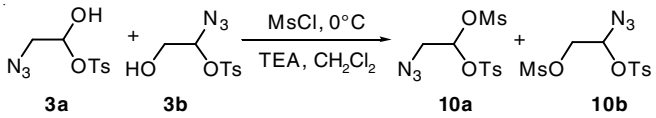
The same mechanism may be applied in the reaction of **8a** with tributylphosphine leading to same results but in higher yields. This was due to easier elimination of tributylphosphine oxide than triphenylphosphine oxide. As regards the effect of solvent, we carried out the reaction in different solvents (Table-2). This reaction proceeded more rapidly in polar, aprotic solvents and the best was acetonitrile.

Reaction of 3-azido-2-((methylsulfonyl)oxy)propyl-4-methylbenzensulfonate) (10a)

Separation of regioisomeric mixture of azides 3a and 3b by mesylation: Interestingly, the mixture of **3a** and **3b** was converted by mesylation of the free hydroxyl group (**Scheme-V**). This reaction afforded a mixture of 3-azido-2-((methylsulfonyl)oxy)propyl-4-methylbenzene-sulfonate) **10a** and 2-azido-propane-1,3-diyl *bis*(4-methyl benzensulfonate)



Scheme-IV: Staudinger reaction of **8a**



Scheme-V: Mesylation of mixture of **3a** and **3b**

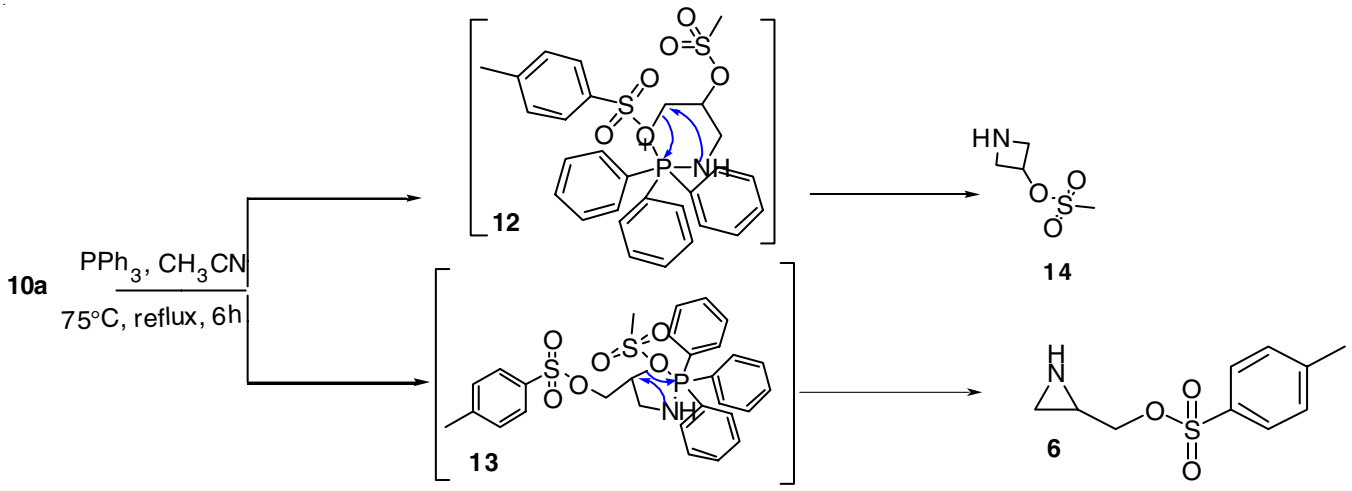
10b that could be separated by column chromathography using a mixture of CH_2Cl_2:MeOH (9:1) as eluent.

Conversion of **10a** to the aziridine **6** (**Scheme-VI**) required moderate heating and ran smoothly in refluxing acetonitrile over 3 h. With the same mechanism shown previously, the reactivity of oxygen with mesyl group was more reactive than the oxygen with the tosyl group, giving the aziridinetosylate in high yield through the oxaphospholidine **13**. Both **6** and **14** were purified by chromatography to afford the expected products in good yield (71 %).

Azide **10a** was also reacted with PBu_3 with aim to investigating the reactivity of both oxygen atoms present on the azide. No difference was observed between PPh_3 and PBu_3, except that PBu_3 oxide was more easily removed only by washing with ether than PPh_3 oxide and yields were higher. The same strategy was followed with different solvents, acetonitrile being the more indicated and same products were obtained in relatively short time and in good yields.

Conclusion

A practical method is developed for the resolution of the mixture of regioisomers of azido-diols by converting the synthetic intermediates into tosylates or mesylates which could not be separated. Besides experimental conditions such as solvents and temperature were important in the control of yields and rate of reactions. This methodology was extremely efficient and was based on the differences of reactivities between the two oxygen atoms of azido-diol toward phosphorus atoms in phosphines. Those differences were crucial in the formation of aziridines and azetidines during ring closure.



Scheme-VI: Staudinger reaction of **10a**

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