SYNTHESIS OF SOME DIOL DERIVATIVES AS POTENTIAL REAGENTS IN STEROID CHEMISTRY

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The multistage syntheses of the p-toluenesulphonyloxy esters [1-benzyloxy-4-p-toluenesulphonyloxybutane (3a), 1-benzyloxy-6-p-toluenesulphonyloxyhexane (3b) and 1-benzyloxy-10-p-toluenesulphonyloxydecane (3c)], alkyl chlorides [1-benzyloxy-4-chlorobutane (4a), 1-benzyloxy-6-chlorohexane (4b) and 1-benzyloxy-10-chlorodecane (4c)], as well as alkyl iodides [1-benzyloxy-4-iodobutane (5a), 1-benzyloxy-6-iodohexane (5b) and 1-benzyloxy-10-iododecane (5c)] with the terminal O-benzyl groups starting from 1,4-butanediol (1a), 1,6-hexanediol (1b) and 1,10-decanediol (1c) were carried out. The possibilities of formation and addition of the corresponding Grignard reagent to the C-17 carbonyl group of dehydroepiandrosterone were investigated.

KEY WORDS: 1,4-butanediol, 1,6-hexanediol and 1,10-decanediol derivatives

INTRODUCTION

The possibility of rendering low molecular weight steroids antigenic by coupling them to proteins, prompted the synthesis of different steroid haptens for immunoassays (1-8). Clutton et al. (9) have applied the hapten principle to prepare thyroxyl derivatives of proteins and then demonstrated that these elicited antisera capable of inhibiting the physiological action of thyroglobulin. Previous attempts to apply this principle to steroids have been unsuccessful, but later a number of radioimmunoassay systems have been developed for the determination of steroid hormones.

The aim of this work was to obtain some derivatives of 1,4-butanediol, 1,6-hexanediol and 1,10-decanediol as potential reagents for the synthesis of some novel steroidal haptens.

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All mentioned diols were transformed into monohalogen derivatives and could serve for linking with steroids.

**EXPERIMENTAL**

NMR spectra were taken on a Bruker AC 250E spectrometer operating at 250 MHz (proton) and 62.9 MHz (carbon), using standard Bruker software; the tetramethylsilane peak (δ 0.00) was used as reference in CDCl₃ for ¹H NMR, whereas the central carbon line of chloroform-d was set at 77.0 ppm for carbon-13 NMR. The extracts were dried over anhydrous sodium sulphate and removal of solvents was carried out under reduced pressure. All reagents used were analytical grade commercially available substances.

**General procedure for the synthesis of compounds 2a-2c**

A mixture consisting of 1,n-alkanediols \[ n = 4 \; (1a; \; 1.0 \; ml, \; 12 \; mmol); \; n = 6 \; (1b; \; 1.0 \; g, \; 8.5 \; mmol) \; and \; n = 10 \; (1c; \; 1.0 \; g, \; 5.7 \; mmol) \], benzyl chloride (0.6 ml, 5.2 mmol) and potassium hydroxide (0.52 g, 9.2 mmol) in anhydrous dioxane (7 ml, for 2a and 2b) or in a mixture of anhydrous dioxane-dimethyl sulphoxide (1:1; 10 ml, for 2c) was refluxed with stirring for 3h. After cooling and filtration, the mixture was diluted with water (10 ml) and extracted with dichloromethane. The obtained crude products were purified on a silica gel column.

**4-Benzyl oxy-1-butanol (2a)**

According to the general procedure as described above, crude compound of 2a was obtained from 1a. Pure compound 2a was obtained after column chromatography (toluene-EtOAc, 1:1), as an oil, in a yield of 43%. ¹H NMR (CDCl₃, δ): 1.69 (m, 4H, H-2, H-3); 3.52 (t, 2H, J=5.0 Hz, H-4); 3.62 (t, 2H, J=7.5 Hz, H-1); 4.52 (s, 2H, Bn); 7.26-7.36 (several signals, 5H, Ar H). ¹³C NMR (CDCl₃, δ): 26.53, 29.94, 62.48, 70.24, 72.93, 127.53-128.32 (5Ar H), 138.04 (Ar H).

**6-Benzyl oxy-1-hexanol (2b)**

Crude compound 2b was prepared from 1b under the same experimental conditions as described above. Pure compound 2b was obtained after column chromatography (toluene-EtOAc, 3:1), as an oil, in a yield of 39%. ¹H NMR (CDCl₃, δ): 1.51 (2m, 8H, H-2, H-3, H-4, H-5); 3.47 (t, 2H, J=5.0 Hz, H-6); 3.63 (t, 2H, J=7.5 Hz, H-1); 4.50 (s, 2H, Bn); 7.26-7.35 (several signals, 5H, Ar H). ¹³C NMR (CDCl₃, δ): 25.56, 29.99, 29.69, 32.69, 62.90, 70.32, 72.88, 127.47-128.32 (5Ar H), 138.63 (Ar H).

**10-Benzyl oxy-1-decanol (2c)**

According to the above general procedure, before diluting the reaction mixture with water, dimethyl sulphoxide was removed by vacuum distillation. Pure compound 2c was obtained from 1c after column chromatography (toluene), as an oil, in a yield of 40.5%. ¹H NMR (CDCl₃, δ): 1.56 (m, 16H); 3.47 (t, 2H, J=5.0 Hz, H-10); 3.63 (t, 2H, J=5.0 Hz, H-1); 4.51 (s, 2H, Bn); 7.34-7.43 (several signals, 5H, Ar H). ¹³C NMR (CDCl₃, δ): 25.68,
General procedure for the synthesis of compounds 3a-3c and 4a-4c

n-Benzylxoy-1-alkanols \([n = 4 \ (2a; \ 0.9 \ g, \ 5.1 \ mmol); \ n = 6 \ (2b; \ 0.1 \ g, \ 0.55 \ mmol)\) and \(n = 10 \ (2c; \ 0.8 \ g, \ 3.1 \ mmol)\) were dissolved in absolute pyridine (10, 4 or 8 ml) and solutions were left at 0°C for 15-20 min. After that a cooled solution (0°C) of \(p\)-toluene sulphonyl chloride (2.8 g, 14.7 mmol for \(2a\); 0.3 g, 1.63 mmol for \(2b\) and 1.8 g, 9.2 mmol for \(2c\)) in absolute pyridine (4 or 8 ml) was added dropwise, and the mixture was stirred for 12 h at room temperature. When the reaction was completed, ice was added and the mixture was stirred for 30 min. The mixture was then poured into ice (300 g), cold HCl (1:1) was added to pH 4-5 and extracted with dichloromethane. The extract was dried, and after evaporation of solvent it was chromatographed on silica gel column using toluene as eluent.

1-Benzylxoy-4-p-toluene sulphonyloxybutane (3a) and 1-benzyloxy-4-chlorobutane (4a)

By following the general procedure, pure compounds 3a (yield 41%) and 4a (yield 19.5%) were obtained as oils.

Compound 3a: \(^1\)H NMR (CDCl\(_3\), \(\delta\)): 1.66 (2m, 4H, H-2, H-3); 2.35 (s, 3H, Ts); 3.37 (t, 2H, J=2.5 Hz, H-1); 4.03 (t, 2H, J=2.5 Hz, H-4); 4.41 (s, 2H, Bn); 7.27-7.80 (several signals, 9H, Ar H). \(^{13}\)C NMR (CDCl\(_3\), \(\delta\)): 20.81 (Ts), 25.26, 25.96, 68.61, 69.90, 72.04, 126.77-144.05 (12Ar H).

Compound 4a: \(^1\)H NMR (CDCl\(_3\), \(\delta\)): 1.92 (2m, 4H, H-2, H-3); 3.55-3.64 (m, 2H, H-1, H-4); 4.58 (s, 2H, Bn); 7.40-7.45 (several signals, 5H, Ar H). \(^{13}\)C NMR (CDCl\(_3\), \(\delta\)): 26.65, 29.12, 44.43, 68.86, 72.29, 127.02-127.86 (5Ar H), 138.18 (Ar H).

1-Benzylxoy-6-p-toluene sulphonyloxyhexane (3b) and 1-benzyloxy-6-chlorohexane (4b)

By following the general procedure, pure compounds 3b as an unstable oil (yield 47%) and 4b as an oil (yield 22%) were obtained from compound 2b.

Compound 3b: \(^1\)H NMR (CDCl\(_3\), \(\delta\)): 2.45 (s, 3H, Ts); 3.45 (t, 2H, J=5.0 Hz, H-1); 4.02 (t, 2H, J=5.0 Hz, H-6); 4.50 (s, 2H, Bn); 7.33-7.85 (several signals, 9H, Ar H). \(^{13}\)C NMR (CDCl\(_3\), \(\delta\)): 21.68 (Ts), 25.26, 25.63, 28.84, 29.53, 70.17, 70.69, 72.94, 127.05-144.77 (12Ar H).

Compound 4b: \(^1\)H NMR (CDCl\(_3\), \(\delta\)): 1.75 (2m, 4H, H-2, H-3, H-4, H-5); 3.49-3.54 (m, 2H, H-1, H-6); 4.52 (s, 2H, Bn); 7.24-7.40 (several signals, 5H, Ar H). \(^{13}\)C NMR (CDCl\(_3\), \(\delta\)): 44.98, 70.14, 72.84, 127.45-128.29 (5Ar H), 138.54 (Ar H).

1-Benzylxoy-10-p-toluene sulphonyloxydecane (3c) and 1-benzyloxy-10-chlorodecane (4c)

Compounds 3c (yield 39%) and 4c (yield 14%) were obtained following the above general procedure.

Compound 3c: \(^1\)H NMR (CDCl\(_3\), \(\delta\)): 1.44 (2m, 16H), 2.45 (s, 3H, Ts); 3.46 (t, 2H, J=7.5 Hz, H-1); 4.01 (t, 2H, J=7.5 Hz, H-10); 4.50 (s, 2H, Bn); 7.28-7.81 (several signals, 9H, Ar H). \(^{13}\)C NMR (CDCl\(_3\), \(\delta\)): 21.62 (Ts), 25.30, 26.15, 28.79, 28.89, 29.29, 29.39, 29.74, 70.48, 70.68, 72.85, 127.46-144.59 (12Ar H).
Compound 4c: $^1$H NMR (CDCl$_3$, $\delta$): 3.49 (m, 2H, H-1, H-10); 4.49 (s, 2H, Bn); 7.29-7.34 (several signals, 5H, Ar H). $^{13}$C NMR (CDCl$_3$, $\delta$): 26.13, 26.83, 28.82, 29.35, 29.38, 29.42, 29.72, 32.59, 45.11, 70.44, 72.81, 127.40-128.28 (5Ar H), 138.65 (Ar H).

1-Benzyl-4-iodobutane (5a)

Compound 3a (0.55 g, 1.65 mmol) was dissolved in ethyl methyl ketone, sodium iodide (1.2 g, 8.3 mmol) was added and the mixture was refluxed with stirring for 2 h. The reaction mixture was poured into water (10 ml) and extracted with dichloromethane. The extract was washed with saturated aqueous sodium sulphite (10 ml), dried and evaporated. The residue was chromatographed on a silica gel column using toluene as an eluent, affording compound 5a (yield 83%), as an oil. $^1$H NMR (CDCl$_3$, $\delta$): 1.89 (2m, 4H, H-2, H-3); 3.25 (t, 2H, J=7.5 Hz, H-4); 3.55 (t, 2H, J=4.0 Hz, H-1); 4.56 (s, 2H, Bn); 7.36-7.43 (several signals, 5H, Ar H). $^{13}$C NMR (CDCl$_3$, $\delta$): 6.81, 30.11, 30.34, 68.71, 72.58, 127.27-138.15 (6Ar H).

1-Benzyl-6-iodohexane (5b) and 1,6-dibenzyloxyhexane (6b)

Compound 2b (0.1 g, 0.5 mmol) was dissolved by heating in hexane (2 ml), red phosphorus (0.005 g, 0.2 mmol) and iodine (0.06 g, 0.2 mmol) were added, and the mixture was heated with stirring at 40-50°C for 30 min. After that, the mixture was poured into water (10 ml) and extracted with dichloromethane. The extract was washed with saturated aqueous sodium sulphite, dried and evaporated. The obtained crude products were chromatographed on a silica gel column using toluene as eluent, affording compounds 5b (yield 10.5%) and 6b (yield 21%) as oils.

Compound 5b: $^1$H NMR (CDCl$_3$, $\delta$): 1.42 (m, 4H, H-3, H-4); 1.63 (m, 2H, H-5); 1.83 (m, 2H, H-2); 3.20 (t, 2H, J=7.5 Hz, H-6); 3.48 (t, 2H, J=5.0 Hz, H-1); 4.52 (s, 2H, Bn); 7.27-7.40 (several signals, 5H, Ar H). $^{13}$C NMR (CDCl$_3$, $\delta$): 7.07, 25.15, 29.51, 30.27, 33.43, 70.16, 72.88, 127.48-128.36 (5Ar H), 138.55 (Ar H).

Compound 6b: $^1$H NMR (CDCl$_3$, $\delta$): 1.29-1.36 (m, 4H); 1.54-1.59 (m, 4H); 3.40 (t, 4H, J=7.5 Hz, H-1, H-6); 4.44 (s, 4H, 2Bn); 7.18-7.29 (several signals, 10H, Ar H). $^{13}$C NMR (CDCl$_3$, $\delta$): 26.03, 29.69, 70.35, 72.82, 127.43-128.30 (10Ar H), 138.65 (2Ar H).

1-Benzyl-10-iododecane (5c) and 1,10-dibenzyloxydecane (6c)

Method a: A mixture consisting of compound 3c (0.10 g, 0.2 mmol), ethyl methyl ketone (5 ml) and sodium iodide (0.23 g, 1.5 mmol) was refluxed with stirring for 1 h. After that, the reaction mixture was treated as described in the procedure for preparation of compound 5a. Compound 5c (yield 75%) was obtained as a yellow oil.

Method b: Following the same procedure as described in Method a, except for using acetone (5 ml) as solvent, compound 5c was obtained in a yield of 65%.

Method c: Iodine (0.14 g, 0.5 mmol) and phosphorus (0.05 g, 1.7 mmol) were added to hexane (2 ml), and the mixture was heated to 40-50°C. Compound 2c (0.1 g, 0.4 mmol) in hexane (2 ml) was added dropwise and the mixture was stirred for 30 min. at room temperature. After that, the reaction mixture was poured into water (10 ml) and extracted with dichloromethane. The extract was washed with saturated aqueous sodium sulphite (10 ml), dried and evaporated. The obtained crude products were separated on a silica
gel column using toluene as eluent, affording compounds \(5c\) (yield 18\%) and \(6c\) (yield 22\%) as oils.

Compound \(5c\): \(^1\)H NMR (CDCl\(_3\), \(\delta\)): 1.51 (m, 2H, H-9); 1.74 (m, 2H, H-2); 3.11 (t, 2H, J=7.5 Hz, H-10); 3.39 (t, 2H, J=7.5 Hz, H-1); 4.43 (s, 2H, Bn); 7.20-7.29 (several signals, 5H, Ar H); \(^{13}\)C NMR (CDCl\(_3\), \(\delta\)): 7.32, 26.16, 28.50, 29.33, 29.40, 29.44, 29.75, 30.48, 33.54, 70.49, 72.85, 127.44-128.32 (5Ar H), 138.70 (Ar H).

Compound \(6c\): \(^1\)H NMR (CDCl\(_3\), \(\delta\)): 3.47 (t, 4H, J=7.5 Hz, H-1, H-10); 4.51 (s, 4H, 2Bn); 7.30-7.36 (several signals, 10H, Ar H).

RESULTS AND DISCUSSION

The starting compounds in the synthesis of the \(p\)-toluenesulphonyloxy esters \(3a-3c\) [1-benzyloxy-4-\(p\)-toluenesulphonyloxybutane (\(3a\)), 1-benzyloxy-6-\(p\)-toluenesulphonyloxyhexane (\(3b\)) and 1-benzyloxy-10-\(p\)-toluenesulphonyloxydecane (\(3c\))], the chlorides \(4a-4c\) [1-benzyloxy-4-chlorobutane (\(4a\)), 1-benzyloxy-6-chlorohexane (\(4b\)) and 1-benzyloxy-10-chlorodecane (\(4c\))], iodides \(5a-5c\) [1-benzyloxy-4-iodobutane (\(5a\)), 1-benzyloxy-6-iodohexane (\(5b\)) and 1-benzyloxy-10-iododecane (\(5c\))] were 1,4-butanediol (\(1a\)), 1,6-hexanediol (\(1b\)) and 1,10-decanediol (\(1c\)). In the first step they were transformed into 4-benzyloxy-1-butanol (\(2a\)), 6-benzyloxy-1-hexanol (\(2b\)) and 10-benzyloxy-1-decanol (\(2c\)) with the aid of benzyl chloride in dioxane or dimethylsulphoxide as solvent, and in the presence of potassium hydroxide (Scheme 1). The corresponding yields of \(2a\), \(2b\) and \(2c\) were 43\%, 39\% and 41\% respectively. In the second step, with the aid of \(p\)-toluenesulphonyl chloride in absolute pyridine as solvent, the benzyl ethers were transformed into 1-benzyloxy-4-\(p\)-toluenesulphonyloxybutane (\(3a\)), 1-benzyloxy-6-\(p\)-toluenesulphonyloxyhexane (\(3b\)) and 1-benzyloxy-10-\(p\)-toluenesulphonyloxydecane (\(3c\)), the respective yields being 41\%, 47\% and 39\%. The sideproducts of tosylation were 1-benzyloxy-4-chlorobutane (\(4a\)) in a yield of 19.5\%, 1-benzyloxy-6-chlorohexane (\(4b\)) in a yield of 22\% and 1-benzyloxy-10-chlorodecane (\(4c\)) in a yield of 14\%. With sodium iodide in ethyl methyl ketone compound \(3a\) afforded alkyl iodide \(5a\) in a yield of 83\%, whereas the tosylate \(3c\) under the same reaction conditions gave the alkyl iodide \(5c\) in a yield of 75\% (Scheme 1).

![Scheme 1](image_url)

**Scheme 1.** \(a\) BnCl, KOH, dioxane; \(b\) BnCl, KOH, dioxane-DMSO (1:1); \(c\) TsCl, Py; \(d\) NaI, EtOMe or MeCOMe
By the reaction of the tosylate 3b with sodium iodide under the same conditions a complex reaction mixture was obtained from which the iodide 5b could not be isolated. However, the alkyl iodide 5b was formed in a direct reaction of the benzyl ether 2b, iodine and red phosphorus in hexane as solvent in a yield of 10.5% (Scheme 2).

Scheme 2.  a) I₂, P, hexane

The main product of this reaction was 1,6-dibenzylhexane 6b in a yield of 21%. The alkyl iodide 5c was also formed in this direct procedure from compound 2c, in a yield of 18%, whereas the main reaction product, 1,10-dibenzylxy decane (6c), was obtained in a yield of 22% (Scheme 2).

The assumed mechanism of the formation of 6b and 6c includes the intermediate formation of the anions 2b', 2c', 5b' or 5c' which gave nucleophilic benzylxy anion by E₁ mechanism, proved in the case of PhCH₂OEt (10) (Scheme 3). The anion –OPI₂ was formed in the process of obtaining 5b and 5c from 2b and 2c according to the well known mechanism.

Scheme 3

The investigations showed that the obtained alkyl iodides 5a-5c are mainly unsuitable for the preparation of the corresponding Grignard reagents and their addition to the C-17 carbonyl group of dehydroepiandrosterone (DA). Namely, the main reaction is the reduction of the mentioned carbonyl group of DA, or the reagent is transformed into the corresponding dibenzyl ether, which diminishes or hinders the possibility of formation of the corresponding Grignard reagent.

CONCLUSION

This work was concerned with the two- and three-step syntheses of 1-benzyloxy-4-iodobutane (5a) and 1-benzyloxy-10-iododecane (5c), as well as the two-step synthesis of
1-benzyloxy-6-iodohexane (5b) starting from 1,4-butanediol (1a), 1,6-hexanediol (1b) and 1,10-decanediol (1c). Unexpectedly, alkyl chlorides 4a-4c, as well as dibenzyloxy alkanes 6b and 6c, were obtained.

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REFERENCES

СИНТЕЗА ОДАБРАНИХ ДЕРИВАТА ДИОЛА КАО ПОТЕНЦИЈАЛНИХ РЕАГЕНАСА У СТЕРОИДНОЈ ХЕМИЈИ

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Изведена је вишепаца синтеза \( p \)-толуенсулфонилокси естара 3a-3c [1-бензилокси-4-p-толуенсулфонилоксипропана (3a), 1-бензилокси-6-p-толуенсулфонилоксихексана (3b), 1-бензилокси-10-p-толуенсулфонилоксигексана (3c)], алкил-хлорида 4a-4c [1-бензилокси-4-хлорбутана (4a), 1-бензилокси-6-хлорхексана (4b), 1-бензилокси-10-хлордекана (4c)] као и алкил-јодида 5a-5c [1-бензилокси-4-јодбутана (5a), 1-бензилокси-6-јодхексана (5b), 1-бензилокси-10-јоддекана (5c)], са терминалном О-бензил групом, полазећи од 1,4-бутандиола (1a), 1,6-хександиола (1b) и 1,10-декандиола (1c). Испитана је могућност добијања и адитије одговарајућих Грињарових реагенаса на С-17 карбонилну групу дехидроепиандростерона.

У првој фази синтезе диоли 1a-1c су преведени у одговарајуће монобензилете 2a-2c [4-бензилокси-1-бутанол (2a), 6-бензилокси-1-хексанол (2b), 10-бензилокси-1-деканол (2c)], који су у реакцији са \( p \)-толуенсулфонил-хлоридом дали естере 3a-3c. Као споредни производи у реакцији естерицијације добијени су хлориди 4a-4c. Дејством натријум-јодида на једињење 3a добијен је алкил-јодид 5a, док је тозилат 3c дао производ 5c. Алкил-јодид 5b је добијен из бензилета 2b дејством јода у присуству црвеног фосфора.

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