The Use of Polymer Supports in Organic Synthesis. II.[1] The Syntheses of Monoethers of Symmetrical Diols

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An insoluble polymer support system was used as a unique method of blocking one functional group of a completely symmetrical difunctional compound. The monotetrahydropyranyl and monotrityl ethers of the symmetrical diols, HO—$(CH_2)_n$—OH, where $n = 2, 4, 6, 8$, and 10, were prepared. Reaction conditions for the preparation of the monotetrahydropyranyl ether of 1,10-decanediol were optimized.

Un système impliquant un support polymérique insoluble a été utilisé pour bloquer un groupe fonctionnel d'un composé difonctionnel complètement symétrique. Les éthers monotétrahydropyranylé et monotritylé des diols symétriques HO—$(CH_2)_n$—OH, où $n = 2, 4, 6, 8$, et 10, ont été préparés. Les conditions expérimentales pour la préparation de l'éther monotétrahydropyranylé du décanédiol-1,10 ont été optiminiséa.　　　　　　　　　　　　　　　　　　　　　　　　　　　　　　　　　[Traduit par le journal]

The concept of using an insoluble polymer support as a selective blocking group of one functional group of a completely symmetrical difunctional compound was recently demonstrated (1). In this paper the syntheses of monotetrahydropyranyl and monotrityl ethers of the completely symmetrical diols, HO—$(CH_2)_n$—OH, where $n = 2, 4, 6, 8$, and 10 are described.

The commercially available Merrifield resin (2) (2% cross-linked polystyrene beads with 1.7 mmol of —CH_2Cl groups/g of resin, obtained from Schwarz/Mann) was modified, according to the procedure of Kusama and Hayatsu (3), to an insoluble polymer containing acid chloride groups, (P)—C_6H_4—CH_2COCl (1). The acid chloride 1 contained 0.8 mequiv. Cl/g of polymer as determined by the modified Vollhard procedure (4). Polymer 1 contains only one in six functionalized phenyl groups along the polymer chain and hence the acid chloride polymer 1 acts as a dilute reagent.

In a typical reaction sequence as outlined in Scheme 1, resin 1 and an excess of symmetrical diol, 2a–e, reacted in pyridine to give the resin, 3a–e, in which one of the alcohol groups was attached to the insoluble polymer through an ester linkage.[2] The unreacted excess diol can be
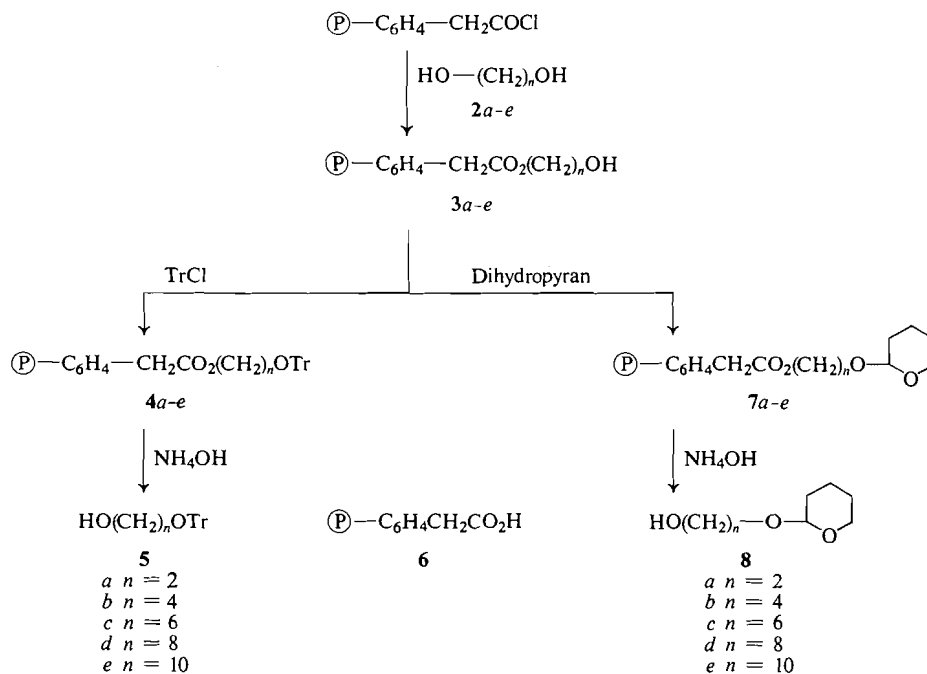
readily recovered by simple filtration of this polymer. This reaction represents a selective blocking of one alcohol group of a completely symmetrical diol. The minimum amount of the diol attached to the polymer was determined by base hydrolysis of 3a–e to give back the starting diol. It is recognized that base hydrolysis of 3a–e could be incomplete even after long reaction times and hence the amount of diol obtained after base hydrolysis represents a minimum amount of diol attached to the polymer. The polymer 3a–e contained approximately 0.05–0.2 mmol of 2a–e per gram.

Reaction of resin esters 3a–e with trityl chloride in pyridine (5, 6) gave the resin trityl ether, 4a–e. Base hydrolysis of 4a–e gave the monotrityl ethers 5a–e in amounts ranging from 0.048 mmol of 5e/g of 4e to as much as 0.087 mmol of 5a/g of 4a. In addition, the acid polymer 6 was recovered.

The monotrityl ethers, 5a–e, were hydrolyzed with 80% acetic acid (5) to give trityl alcohol and the parent diols, 2a–e, in a 1:1 ratio. Elemental analysis and the mass spectral data of 5a–e were entirely consistent with the assigned structures. Ethers, 5a–e gave parent ions in their mass spectra. In addition, all spectra of 5a–e showed a base peak at m/e 243 resulting from the cleavage of the ethers and the formation of the bulky trityl cation. This mode of cleavage of bulky tertiary ethers is well documented (7). The i.r. spectra of 5a–e showed broad O—H absorption at 3450 cm^{-1} and

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[1]For Part I, see ref. 1.

[2]The possibility exists that two adjacent phenyl rings are functionalized and hence both ends of the symmetrical diols, 2a–e, could attach themselves to the polymer. The use of a large excess of diol greatly diminishes the chance of this occurring.

$$\text{(P)}—C_6H_4—CH_2COCl$$

$$\downarrow HO—(CH_2)_nOH$$

$$2a\text{-}e$$

$$\text{(P)}—C_6H_4—CH_2CO_2(CH_2)_nOH$$

3a–e

TrCl | Dihydropyran

$$\text{(P)}—C_6H_4—CH_2CO_2(CH_2)_nOTr$$

4a–e

$$\text{(P)}—C_6H_4CH_2CO_2(CH_2)_nO\text{—}\langle\text{THP}\rangle$$

7a–e

$$\downarrow NH_4OH$$

$$\downarrow NH_4OH$$

$$HO(CH_2)_nOTr$$

$$\text{(P)}—C_6H_4CH_2CO_2H$$

$$HO(CH_2)_n—O\text{—}\langle\text{THP}\rangle$$

5	6	8
a n = 2		a n = 2
b n = 4		b n = 4
c n = 6		c n = 6
d n = 8		d n = 8
e n = 10		e n = 10

SCHEME 1

aromatic absorption at 1600 cm⁻¹. The i.r. spectra of **3a–e** and **4a–e** were uninformative.

The quantity of **5a–e** from **3a–e** was not as high as expected and it was suspected that the bulkiness of the trityl group was inhibiting the base hydrolysis of **4a–e**. In an experiment designed to test this hypothesis resin **4e** was treated with concentrated HCl in dioxane to give the diol **2e** and trityl alcohol in 0.12 mmol/g of **4e**. Thus the yield of the tritylation step is quite high and the moderate quantity of **5e** obtained is likely due to the inefficiency of the base hydrolysis of **4e**. The bulkiness of the trityl group may add to the inefficiency of the final base cleavage reaction resulting in decreased quantities of **5a–e**. Thus some mono trityl ether remains attached to the polymer.

In an attempt to see if polymer **6** was reusable, **6** was converted back to the acid chloride **1**, by treatment with thionyl chloride, and the sequence of reactions repeated using 1,10-decanediol, **2e**, as a model.

The quantity of **5e** obtained from once used polymer was less than 50% of that obtained using fresh polymer **1** (see Experimental). The used polymer **6** was again converted to **1** and the sequence repeated a second time using alcohol **2b**. The yield of **5b** from twice used

polymer was less than 25% of that obtained using fresh polymer **1**. If one considers that base hydrolysis of polymer **4b** is incomplete because of the inefficiency of the base cleavage and perhaps the bulkiness of the trityl group, then it is reasonable to expect that the used polymer **6** has less carboxy groups liberated and hence available for subsequent reactions. It should also be noted that every subsequent recyclization of polymer **6** resulted in a browner polymer.

Thus, in the formation of monotrityl ethers the base cleavage of the ether from the polymer is incomplete resulting in lower yields and the polymer liberated is not highly suitable for regeneration as subsequent cycles result in even lower yields.

The polymer support synthesis of monotrityl ethers of symmetrical diols gave the monoethers in moderate quantities on a mole basis. In order to demonstrate the formation of monoethers of symmetrical diols in higher quantities on a mole basis, it was decided to synthesize the mono-tetrahydropyranyl ethers of the symmetrical diols **2a–e**. The reduced steric requirements of the tetrahydropyranyl group as compared to the trityl group should result in higher yields of monoethers.

Reaction of resin **3a–e** in anhydrous dioxane

with excess dihydropyran, anhydrous sodium sulfate and *m*-benzene-disulfonic acid as a catalyst gave, after 48 h at room temperature,[3] resin 7*a–e*. Subsequent base cleavage of 7*a–e* yielded resin 6 and 8*a–e* in quantities averaging 0.035 mmol/g of 7*a–e*.

The reaction of 3*a–e* with dihydropyran was incomplete as evidenced by the isolation of the parent diols, 2*a–e*, from the base cleavage of 7*a–e*. The monotetrahydropyranyl ethers, 8*a–e*, were separated from the parent diols, 2*a–e*, by preparative t.l.c. on alumina prepared from an aqueous slurry containing 1% sodium bicarbonate. T.l.c. on silica gel, even prepared with sodium bicarbonate always resulted in hydrolysis of 8*a–e* to 2*a–e* and dihydropyran. The pure tetrahydropyrans, 8*a–e* were rechromatographed on alumina containing 1% sodium bicarbonate and pure 8*a–e* showed no evidence of hydrolysis on this adsorbant system, thus showing that the starting diols obtained in the hydrolysis of 7*a–e* were, in fact, due to incomplete reaction of 3*a–e* and not due to hydrolysis of 8*a–e* in the work-up of the reaction.

The monotetrahydropyranyl ethers, 8*a–e*, were hydrolyzed on silica gel to give dihydropyran and the parent diols, 2*a–e*, in a 1:1 ratio. Elemental analysis and the mass spectral data of 8*a–e* were entirely consistent with the assigned structures. Ethers, 8*c–e* exhibited very weak parent ions in their mass spectra, while 8*a–b* showed no parent ions at all. In addition, however, 8*a–e* all exhibited the tetrahydropyranyl cation as the base peaks of the spectra. The weak parent ions and the formation of the tetrahydropyranyl cation is consistent with published data on the mass spectra of tetrahydropyranyl ethers (8).

The i.r. spectra of the monotetrahydropyranylethers 8*a–e* were almost identical to each other; and showed much broader absorptions at 3450 (O—H) and 1080 cm^{-1} (C—O—C) than the diols 2*a–e*. The i.r. spectra of 7*a–e* were uninformative and were not useful for characterization.

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[3]The reaction of diols 2*a–e* with 1 to give 3*a–e* for the preparation of the trityl ethers, 5*a–e*, were conducted partially at higher temperatures (see Experimental). Although more diol became attached to the polymer at higher temperatures, it was felt that the more inaccessable functional groups reacted at these higher temperatures resulting in loss of starting material and deterioration of the polymer.

The resin 6 recovered from the hydrolysis of 7*a–e* was converted back to polymer 1, by treatment with thionyl chloride, and the sequence of reactions leading to 8*e* was repeated. The quantity of 8*e* obtained from once-used polymer was only 50% of that obtained from the fresh polymer and hence polymer 6 generated from the hydrolysis of 7*a–e* is also not a very suitable regenerable polymer and exhibits similar characteristics to polymer 6 regenerated from the hydrolysis of 4*a–e*. Thus the inefficiencies of the base cleavage reaction of 4*a–e* and 7*a–e* and the deterioration of the polymer by SOCl$_2$[4] appear more responsible for the incomplete regeneration of 1 from 6 than the bulkiness of the trityl group of 4*a–e*. One of the drawbacks of organic synthesis on insoluble polymer support systems is the long reaction times involved in the various reactions on the insoluble polymer. It was thus decided to do a time study on the various reactions leading to the formation of 8*e* as a model system.

Polymer 1 was reacted with 2*e* at various times as shown in Table 1. Subsequent base cleavage of the product 3*e* for 48 h gave back the starting diol, 2*e*, in maximum yield for a reaction time of 1 with 2*e* of 48 h showing that for the initial attachment of the diol to the polymer, the standard time of reaction, 48 h, was optimum.

The reaction of 3*e* with dihydropyran for different times was performed. As shown in Table 2, reaction was essentially complete after 24 h instead of the standard reaction time of 48 h. In fact the yield of 8*e*, obtained after base hydrolysis of 7*e* was slightly lower for longer reaction times.

The effect of time on the base hydrolysis of 7*e* was next examined. As indicated in Table 3, base hydrolysis of 7*e* to yield 8*e* was complete after 48 h. Thus the standard conditions were best for the base cleavage step.

Thus a practical general method of synthesizing monotrityl and monotetrahydropyranyl ethers of symmetrical diols has been outlined.

The insoluble polymer support synthesis of monotrityl ethers of symmetrical diols is preferable to the synthesis of the monotetrahydropyranyl ethers of symmetrical diols as they are obtained in higher quantities, while the tetra-

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[4]The polymer turns pale brown on treatment with SOCl$_2$.

TABLE 1. The effect of time on the reaction of 1 with 2e

Amount of 1 (g)	Time of reaction (h)	*Yield of 2e (g)
4.0230	1	0.0189
4.0631	10	0.0219
4.0781	24	0.0303
4.1162	48	0.0382

*Obtained by based hydrolysis of 3e for 48 h.

TABLE 2. The effect of time on the reaction of 3e with dihydropyran

Amount of 3e (g)	Time of reaction (h)	*Yield of 8e (g)
4.0244	2	0.0081
4.0707	10	0.0291
4.0166	24	0.0373
4.0266	48	0.0336

*Obtained by base hydrolysis of 7e for 48 h.

TABLE 3. The effect of time on the base cleavage of 7a–e

Amount of 7e (g)	Time of reaction (h)	Yield of 8e (g)
4.0968	1	0.0098
4.0971	24	0.0305
4.1009	48	0.0386
4.1148	72	0.0385

hydropyranyl ethers are always contaminated by starting diol which must be separated by preparative t.l.c.

The use of insoluble polymers as blocking groups of other symmetrical difunctional organic compounds is in progress using means other than the inefficient base hydrolysis of products from the insoluble polymer. The search for a more regenerable polymer is also under investigation.

Experimental

All melting points were determined on a Kofler hot stage and are uncorrected. The i.r. spectra were recorded on a Unicam SP1000 i.r. spectrophotometer using neat compounds or Nujol mulls. Mass spectra were recorded on a Hitachi-Perkin-Elmer RMU-6 mass spectrometer. Silica gel, and alumina, prepared with a 1% $NaHCO_3$ aqueous slurry, were used for thin and thick-layer chromatography. Microanalyses were performed by Dr. C. Daessle of Montreal and G. Gygli of Toronto.

Acid Chloride Resin 1

The Merrifield resin (2) (2% cross-linked polystyrene beads having 1.7 mmol of —CH_2Cl groups/g of resin was obtained from Schwarz/Mann and converted to 1

according to the procedure of Kusama and Hayatsu (3). Resin 1 contained 0.8 mmol Cl/g of polymer as determined by the modified Vollhard procedure (4).

Preparation of the Alcohol Resins, 3a–e

A typical example is given for the preparation of resin 3e. A suspension of 4.12 g of (P)—C_6H_4—CH_2—$COCl$ in 30 ml of anhydrous pyridine and 2.71 g of 1,10-decanediol, 2e, was stirred under exclusion of moisture ($CaCl_2$-tube) at room temperature for 24 h and at 100 °C for 24 h. The resin was collected by filtration and washed three times with pyridine, three times with pyridine–water (1:1), three times with water, three times with ethanol, and finally three times with ether.

Preparation of the Trityl Resins, 4a–e

A standard procedure is given for the synthesis of 4e. A mixture of 3.02 g of resin 3e and 2.0 g of chlorotriphenylmethane in 40 ml of anhydrous pyridine were stirred for 48 h at room temperature under exclusion of moisture ($CaCl_2$-tube). The resin was then collected by filtration and washed four times with pyridine, three times with pyridine–water (3:1), three times with pyridine–water (1:1), six times with water, three times with ethanol–water (1:1), once with acetone, three times with ethanol, and at least three times with dry ether.

Release of the Monotritylalcohols, 5a–e, from Resins 4a–e

In a standard procedure, 3.22 g of resin 4e was treated with 20 ml of a 1:1 mixture of dioxane and concentrated ammonia in a stoppered flask with magnetic stirring for 48 h. The resin was filtered and washed six times with water, once with acetone, three times with ethanol, and three times with ether. The aqueous filtrate was extracted with three aliquots of ether. The combined ether extracts were washed six times with water, dried over Na_2SO_4 and evaporated to give a slightly impure oil which was purified by preparative t.l.c. on silica gel (eluant 10% $CHCl_3$ – 90% C_6H_6) to give 0.0645 g of analytically pure 5e (see Table 4 for physical and mass spectra data on 5a–e). No starting diol 2e was detected.

Preparation of the Tetrahydropyranyl Ether Resins 7a–e

In a typical procedure, 4.01 g of resin 3e (prepared by reaction of 1 with 2e for 48 h at room temperature only) was suspended in 30 ml of anhydrous dioxane. Excess dihydropyran (5.00 g) and 0.10 g of m-benzenedisulfonic acid was added as a catalyst. To the mixture was added 2.00 g of anhydrous sodium sulfate to absorb liberated water and the reaction was stirred for 24 h under exclusion of moisture ($CaCl_2$-drying tube). The resin was filtered, neutralized with anhydrous pyridine (to prevent hydrolysis of the monopyranyl ether) and filtered twice. Then the resin was washed twice with pyridine–water (1:1), ten times with water (to remove sodium sulfate), three times with ethanol, and at least three times with dry ether.

Release of the Monotetrahydropyranyl Alcohols, 8a–e, from Resins 7a–e

A suspension of 4.01 g of resin 7e and 30 ml of a 1:1 mixture of dioxane and concentrated ammonium hydroxide was stirred for 48 h at room temperature. The resin was filtered and washed as before in the preparation of 5a–e. An identical work-up as before yielded an impure oil. Preparative t.l.c. on alumina prepared with a 1%

TABLE 4. Physical and mass spectral data of 1-*O*-trityl-1,*n*-alkanediols

| Compound | M.p. (°C) | Yield (mmol/g polymer) | Analysis | | | | Mass spectra m/e M$^+$ (% of base peak) |
| | | | Found | | Calculated | | |
			C	H	C	H	
TrO(CH$_2$)$_2$OH	95–96*	0.087	82.64	6.72	82.89	6.58	3.80
TrO(CH$_2$)$_4$OH	65–67	0.074†	83.17	7.51	83.13	7.23	2.31
TrO(CH$_2$)$_6$OH	68–69	0.085	83.31	7.89	83.33	7.78	0.59
TrO(CH$_2$)$_8$OH	oil	0.072	83.35	8.13	83.51	8.25	5.63
TrO(CH$_2$)$_{10}$OH	oil	0.048‡	83.30	8.64	83.65	8.65	6.87

*Literature 98–100° (6).
†From twice and thrice used polymer only 0.012 and 0.006 mmol/g of 4b respectively were obtained.
‡From once used polymer only 0.019 mmol/g of 4e were obtained.

TABLE 5. Physical and mass spectral data of 1-*O*-tetrahydropyranyl-1,*n*-alkanediols

| Compound 8 | Yield (mmol/g polymer) | Analysis | | | | Mass spectra m/e M$^+$ (% of base peak) |
| | | Found | | Calculated | | |
		C	H	C	H	
a	0.034	57.27	9.44	57.53	9.59	0.00
b	0.027	62.30	10.65	62.07	10.34	0.00
c	0.036	65.35	10.89	65.54	10.92	0.15
d	0.034	67.83	11.30	67.43	11.61	0.35
e	0.036*	69.80	11.63	69.48	11.80	0.26

*From once used polymer only 0.017 mmol of 8e/g polymer 7e was obtained.

slurry of NaHCO$_3$, and using 2:3 benzene – petroleum ether gave 0.0373 g of analytically pure **8e** and 0.0126 g of recovered **2e**. (See Table 5 for physical and mass spectral data on **8a–e**.)

Determination of the Amounts of Diols, 2a–e, on Resins 3a–e

A suspension of 4.11 g of resin **3e** in a 1:1 mixture of dioxane and concentrated ammonium hydroxide was stirred at room temperature for 48 h. The resin was filtered and washed in the same manner as for the release of **8e** from **7e**. An identical work-up as before yielded 0.03 g of **2e**.

Regeneration of Polymer 1 from Polymer 6

The acid resin **6** was treated with thionyl chloride in toluene and refluxed for 24 h with stirring according to Kusama and Hayatsu (3).

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