A Novel Preparative Method for Unsymmetrical Ethers by the Reaction of Cocrystals of Two Similarly Substituted Secondary Alcohols with Toluene-*p*-sulphonic Acid in the Solid State

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Two secondary alcohols form 1 : 1 cocrystals, and treatment of the cocrystal with toluene-*p*-sulphonic acid in the solid state gives unsymmetrical ethers.

Previously we reported some efficient-solid state reactions of alcohols, including the etherification of secondary alcohols.[1] Recently we found that two types of secondary alcohols form 1:1 cocrystals, and treatment of the cocrystal with toluene-*p*-sulphonic acid (TsOH) in the solid state gives unsymmetrical ethers efficiently. We also found that etherification in the solid state which proceeds *via* a carbonium ion intermediate (S_N1 reaction) occurs with retention of the configuration of the alcohol.

Cocrystals of secondary alcohols were prepared by recrystallisation of equimolar amounts of two alcohols from ether. By this method, for example, the cocrystals shown in Table 1 were prepared. Treatment of the powdered cocrystals with TsOH in the solid state at room temperature for 2 h gave ethers in the yields† shown in Table 1. In the case of entry 1, the cross-etherification product was obtained exclusively in addition to small amounts of recovered alcohols. In the case of entries 2–5, the corresponding unsymmetrical ether was produced predominantly. When the etherification reaction was carried out in toluene, the three possible ethers were obtained in yields reflecting statistical product ratios.

Since cocrystallisation can occur by mixing two alcohols in the solid state,[2] preparation of cocrystals by the recrystallisation method described above is not always necessary for the cross-etherification. When two alcohols were mixed well using an agate mortar and pestle for 10 min and then further mixed with TsOH, and the mixture was kept at room temperature for 2 h, unsymmetrical ethers were obtained selectively (Table 2). Since cocrystals of **1a** and 3,3-dimethylbutan-2-ol **5** are too unstable for isolation in a pure state, this mixing method is very useful for the cross-etherification of these compounds (entry 8 in Table 2).

The selective cross-etherification reaction suggests that the two alcohols are arranged in the cocrystal so as to form a pair by hydrogen bonding. The action of TsOH on the pair of

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† Yields of all chiral etherification products except **7** and **11** are for isomeric mixtures (*e.g.* racemate, *meso* compound and diastereoisomer).

Table 1 Yields of products in the solid state reaction of 1 : 1 cocrystals of secondary alcohols with TsOH[a]

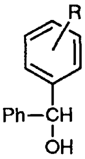
	1 : 1 Cocrystal			Yield of products[b] and recovery (%)[b]				
	Alcohol		M.p.					
Entry	A	B	T/°C	A–B	A–A	B–B	A	B
1	**1a**	**1b**	72	78	0	0	5	1
2	**1a**	**1d**	44	74	8	6	1	2
3	**1d**	**4a**	66	71	2	3	2	3
4	**1a**	**2**	57–58	69	3	4	3	7
5	**1a**	**4a**	55–56	78	2	5	1	1

[a] Reactions were carried out by keeping a mixture of powdered cocrystal and 0.5 mol. equiv. of TsOH at room temperature for 2 h. [b] Isolated yields by column chromatography on silica gel.

Table 2 Yields of products in the etherification reaction of the cocrystals prepared by mixing secondary alcohols in the solid state[a]

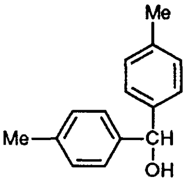
	Secondary alcohol		Yield of products and recovery (%)[b]				
Entry	A	B	A–B	A–A	B–B	A	B
1	**1a**	**1d**	65	15	15	2	3
2	**1a**	**4a**	70	10	7	3	5
3	**1a**	**4b**	60	10	18	2	8
4	**1a**	**1c**	71	10	8	1	2
5	**1d**	**4a**	57	17	15	1	2
6	**4b**	**3a**	58	0	0	0	8
7	**1a**	**3b**	70	0	0	0	0
8	**1a**	**5**	59	0	0	0	0

[a] Reactions were carried out by mixing equimolar amounts of the two alcohols in an agate mortar and pestle for 10 min, and then mixing with 0.5 mol. equiv. of TsOH; and the mixture was kept at room temperature for 2 h. [b] Isolated yields by column chromatography on silica gel.



1

a; R = H
b; R = *o*-Me
c; R = *p*-Bu^t
d; R = *o*-Cl



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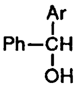
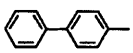


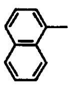
$Ph{-}CH(Ar){-}OH$

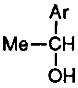
3

a; Ar =



b; Ar =

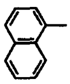




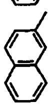
$Me{-}CH(Ar){-}OH$

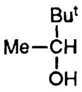
4

a; Ar =



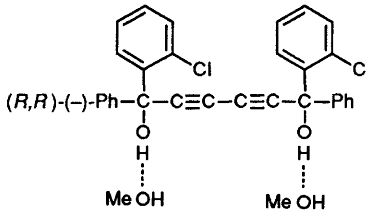
b; Ar =





$Me{-}CH(Bu^t){-}OH$

5



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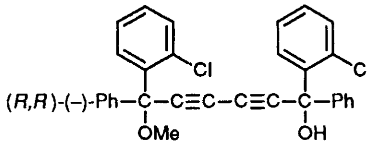
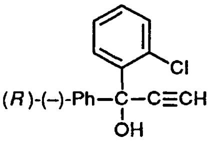


7



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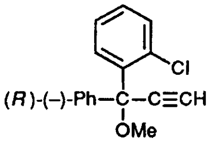

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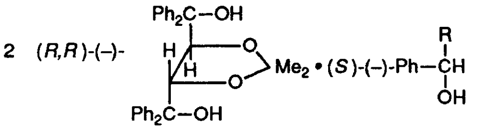
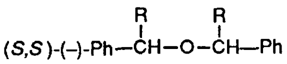


10

a; R = Me
b; R = Et



$(S,S)\text{-}(-)\text{-}Ph{-}CH(R){-}O{-}CH(R){-}Ph$

11

alcohols gives the unsymmetrical ether efficiently and selectively. If this hypothesis is correct, the attack of one alcohol of the pair on the carbonium ion generated by TsOH-catalysed dehydroxylation of the other alcohol should occur from the same side as that from which the hydroxy group is eliminated. This means that the reaction should proceed with retention of the configuration of alcohol. This hypothesis was proved to be correct by the etherification of the 1 : 2 inclusion crystal **6** of (*R*,*R*)-(−)-1,6-diphenyl-1,6-bis(*o*-chlorophenyl)hexa-2,4-diyne-1,6-diol[3] and MeOH in the solid state which gives the (*R*,*R*)-(−)-methoxy derivative **7** in 94% enantiomeric excess (e.e.) {[α]$_D$ −95° (*c* 0.33 in MeOH)}. The optical purity and absolute configuration of **7** were determined by comparison of its optical rotation with that of an authentic sample {[α]$_D$ −101° (*c* 0.24 in MeOH)} prepared by cross-coupling of the (*R*)-(−)-alcohol **8**[4] with the (*R*)-(−)-ether **9**. Optically pure **9** {[α]$_D$ −93° (*c* 0.41 in MeOH)} was prepared by treatment of **8** with NaH followed by MeI. The formation of the monomethoxy derivative **7** instead of the dimethoxy compound in the TsOH-catalysed reaction of **6** is probably due to a difference in strength of binding of the two MeOH molecules in **6**: one binds tightly to the OH group of the diacetylenic diol, and the other loosely through hydrogen-bond formation; the etherification occurs only in the former combination.[5]

Further evidence for the enantioselective etherification of alcohols in the solid state was obtained from the reaction of 1-phenylethanol and 1-phenylpropanol. Because these alcohols are liquids, their solid state etherification was carried out in inclusion complex crystals. Treatment of a 2 : 1 inclusion crystal of (*R*,*R*)-(−)-*trans*-4,5-bis(hydroxydiphenylmethyl)-2,2-dimethyl-1,3-dioxacyclopentane[6] and (*S*)-(−)-1-phenylethanol **10a** with TsOH in the solid state at room temperature for 5 h gave optically pure (*S*,*S*)-(−)-bis(1-phenylethyl) ether **11a** {[α]$_D$ −28° (*c* 0.51 in MeOH)}, but no *meso*-isomer. Similar treatment of the inclusion crystal **10b** of (*S*)-(−)-phenylpropanol gave optically pure (*S*,*S*)-(−)-bis(1-phenylpropyl) ether **11b** {[α]$_D$ −30° (*c* 0.64 in MeOH)}. The optical purity of **11a** and **11b** was elucidated by HPLC using an optically active solid phase, Chiralcel OC.‡

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‡ Chiralcel OC is available from Daicel Industries, Ltd., Himeji, Japan.

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5 An X-ray crystal structure analysis of **6** showed that the two hydrogen bond distances between the OH group of the host and MeOH are 2.635(8) and 2.967(8) Å. The data will be published in detail by T. Fujiwara and F. Toda.

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