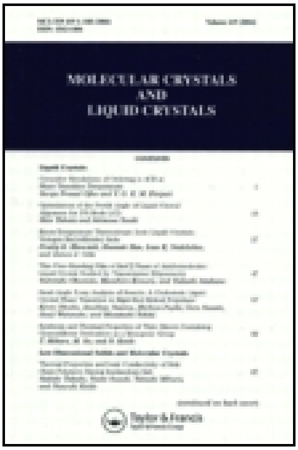

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Selective Etherification of Alcohols in the Solid State

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SELECTIVE ETHERIFICATION OF ALCOHOLS IN THE SOLID STATE

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Abstract Etherification reaction of secondary alcohols proceeded more efficiently in the solid state than in solution. The etherification of two different alcohols in their 1:1 co-crystal gave unsymmetrical ethers selectively.

Keywords: Selective etherification, Solid state reaction, Co-crystals of alcohols, Hydrogen bond, Enantioselective reaction, X-ray structure of alcohols

INTRODUCTION

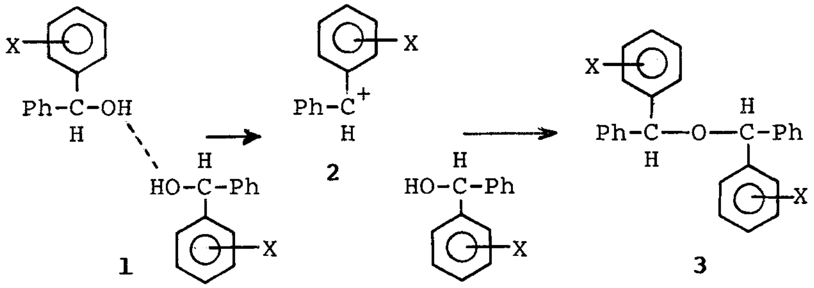
Secondary alcohols assemble themselves in the crystalline state. Treatment of the self-assembled crystal with TsOH in the solid state gave ethers efficiently. The self-assembly occurred between molecules of different alcohols. The 1:1 co-crystal of the different alcohols gave similar unsymmetrical ethers selectively. X-ray crystal structure analysis of the self-assembled crystal showed that two molecules of alcohol are paired through hydrogen bond formation.

RESULTS AND DISCUSSION

In 1990, we found that TsOH-catalyzed etherification of secondary alcohols (**1**) to their ethers (**3**) proceeds much more efficiently in the crystalline state than it does in solution (Table I).[1] X-ray crystal structure analysis of benzhydrol (**1a**), for example, disclosed that two molecules of **1a** are paired through hydrogen bond formation (Scheme 1), and this self-assembly of the two alcohol molecules close to each other accounts for the efficiency of the reaction in the crystal. This observation further suggested to us that the etherification reaction should occur with retention of configuration of the alcohol, since the addition of **1** to the initially generated carbonium ion (**2**) should occur only from the front side, as shown in Scheme 1. In the event, crystal etherification of (-)-**1e** gave optically pure (-)-**3e**.

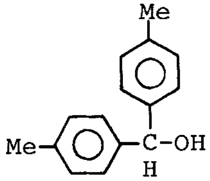
Of considerable interest was the observation that this self-assembly occurred between molecules of different alcohols. For example, **1a** and **1b**, **1a** and **1d**, **1d** and **5a**, **1a** and **4**, and **1a** and **5a** formed 1:1 co-crystal and their etherification in the crystalline state gave the corresponding unsymmetrical ether in predominant yield (Table I). These results suggest that the two types of alcohol molecules are arranged as a pair in each of these co-crystals. This cocrystallization can not only be attained by recrystallization but also by simply mixing the two types of alcohol in the solid state. Thus, mixing the two alcohols together by grinding in an agate mortar and pestle for 10 min, followed by a further grinding with TsOH gave, after standing at room temperature for 2 h, predominantly the unsymmetrical ether (Table II).[2] These observation could be extended to mixture of three alcohols. For example, 1:1:1 co-crystals of **1b**, **5b**, and **6a**, and of **1d**, **5a**, and **5b**, could be formed, with melting points of 35-36 °C and 32 °C, respectively. The latter system is unstable and is transformed into a 1:1 co-crystal of **1d** and **5a** by further recrystallization. Treatment of the 1:1:1 co-crystal (mp 35-36 °C) with solid TsOH gave the mixed ether of **1b** and **5b** selectively, while similar treatment of the 1:1:1 crystal (mp 32 °C) gave the mixed ether of **1d** and **5b**. When these reactions were carried out in solution in toluene a complex mixture of ethers was obtained.

It is of considerable interest that even simple secondary alcohols such as **1** and **4-6** have high molecular recognition and form self-assembled co-crystals selectively. The high level of selectivity in this simple etherification reaction suggests that we may only be at the begining of a new field of chemistry involving reactions in the crystalline state.



a: X=H; **d:** X=o-Cl
b: X=o-Me; **e:** X=m-Me
c X=p-tBu;

Scheme 1



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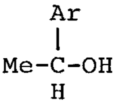
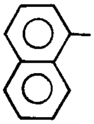


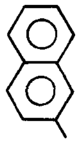
$\mathrm{Me-\underset{H}{\overset{Ar}{C}}-OH}$

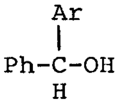
5

a: Ar=



b: X=

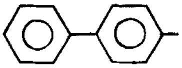




$\mathrm{Ph-\underset{H}{\overset{Ar}{C}}-OH}$

6

a: Ar=



b: Ar=

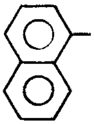


TABLE I. Yield of products in the solid state reaction of 1:1 co-crystal of secondary alcohols with TsOH[a]

1:1 Co-crystal			Yield (%) of products[b]		
alcohol		Mp/°C			
A	**B**		**A–B**	**A–A**	**B–B**
1a	**1b**	72	78	0	0
1a	**1d**	44	74	8	6
1d	**5a**	66	71	2	3
1a	**4**	57–58	69	3	4
1a	**5a**	55–56	78	2	5

[a] Reactions were carried out by keeping a mixture of powdered co-crystal and half-molar amount of TsOH at room temperature for 2 h. [b] Isolated yields by column chromatography on silica gel.

TABLE II. Yield of products in the etherification reaction of the co-crystal prepared by mixing secondary alcohols in the solid state[a]

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

[a] Reactions were carried out by mixing equimolar amounts of two different alcohols with an agate mortar and pestle for 10 min, followed by further mixing with half-molar amount of TsOH. [b] Isolated yields by column chromatography on silica gel.

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