Tetrahedron: Asymmetry Vol. 4, No. 8, pp. 1771-1774, 1993
Printed in Great Britain

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Enantioselective Michael Additions to Enones in Their Inclusion Crystals with Optically Active Host Compounds

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(*Received in UK* 12 *May* 1993)

Abstract: Some enantioselective Michael addition reactions in the solid state are reported. For example, when a powdered 1:1 inclusion crystal of 2-cyclohexenone (**2**) with (R,R)-(-)-*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[5.4]decane (**1**) in the presence of benzyltrimethylammonium hydroxide (**4**) as a base is treated with 2-mercaptopyridine, 2-mercaptopyrimidine, and 4,6-dimethyl-2-mercaptopyrimidine it gives the corresponding Michael addition product in 80, 78, and 74% ee, respectively. Some other enantioselective Michael addition reactions in the solid state are also reported.

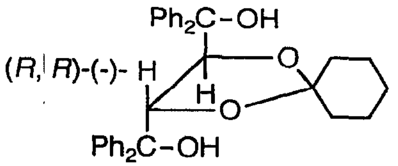
Enantioselective Michael addition of thiols to enones is a useful reaction in synthesis of sex pheromones[1] and terpenes.[2] For example, Mukaiyama [3,4] and Wynberg[5,6] have reported enantioselctive Michael addition reactions of thiols to 2-cyclohexenone (**2**) and maleic acid esters in the presence of chiral bases such as cinchona alkaloids and optically active amino alcohols.

We have been studying enantioselective solid state reactions such as ketone reductions[7] and Wittig-Horner reactions[8] in inclusion crystals with optically active host compounds. We have now applied these enantioselctive reactions to Michael addition reactions and have found that Michael addition reaction of thiols to **2** included in the optically active host compound, (R,R)-(-)-*trans*-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro-[5.4]decane (**1**) in the presence of a catalytic amount of aqueous solution of benzyltrimethylammonium hydroxide (**4**) gives optically active addition product of high optical purity. We have also found that **5** adds enantioselectively to 3-methyl-3-buten-2-one (**8**) in its inclusion crystal with **1** (**9**) and that cycloalkanones (**13-16**) also add enantioselectively to methyl vinyl ketone in its inclusion crystal with **1** (**12**) under similar reaction conditions.

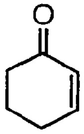
A 1:1 inclusion crystal of **1**[9] and **2** (**3**) was obtained as colourless needles by keeping a solution of **1** (5 g, 10.2 mmol) and **2** (1.2 g, 12.5 mmol) in benzene (20 ml)-hexane (20 ml) at room temperature for 12 h (5.1 g, 83% yield, mp 125-126 C). A mixture of powdered **3** (0.5 g, 0.83 mmol), 2-mercaptopyridine (**5a**) (0.11 g, 1.0 mmol), and 40% aqueous solution of **4** (0.07 g, 0.17 mmol) was irradiated with ultrasound[10] for 1 h at room temperature, and then kept for 23 h. The reaction mixture was extracted with $CHCl_3$ and the $CHCl_3$ solution was chromatographed on silica gel to give (+)-**6a** as an oil in 80% ee (0.088 g, 51% yield, $[a]_D$ +66.0 (*c* 0.55, MeOH)). The same reaction of **3** with 2-mercaptopyrimidine (**5b**), 4,6-dimethyl-2-mercaptopyrimidine (**5c**), and 2-mercaptothiazoline (**5d**) gave (+)-**6b** in 78% ee, (+)-**6c** in 74% ee, and (+)-**6d** of unknown optical purity, respectively in the yields shown in Table 1. Optical purities of **6a-c** were determined by HPLC on the chiral solid phase, Chiralpak AS.[†] However, the optical purity of **6d** was not determined.

Nevertheless, reactions of **3** with benzenethiol (**5e**) and 2-toluenethiol (**5f**) under the same conditions applied for **5a-d** gave rac-**6e** and **6f**, respectively (Table 1). The nitrogenatom on the ring of **5** seems important for the enantioselective Michael reaction. A plausible interpretation for the role of the nitrogenatom is that the unshared electrons on the nitrogenatom of the sulfide anion derived from **5** associaste with the ammonium ion derived from **4** to form the sterically bulky complex (**7**) (Scheme 1). The steric course of attack of the sulfide anion of **7** to **2** in **3** is well controlled by the bulky ammonium ion moiety of **7**; whereas enantioselectivity of the Michael addition in the presence of other simple bases is lower. For example, treatment of **3** with **5a** in the presence of Et_3N and *t*BuOK gave (+)-**6a** of 72% ee and 66% ee in 36% and 23% yields, respectively. Michael addition of **5e** to **2** in its β-cyclodextrin complex in a water suspension has been reported to proceed enantioselectively, although the optical purity of (-)-**6e** thus obtained was only 30% ee.[11]

Michael addition of **5** to 3-methyl-3-buten-2-one (**8**) in its inclusion crystal with **1** also occurred enantioselectively. When a solution of **1** (2 g, 4 mmol) and **8** (1 g, 12 mmol) in cyclohexane (50 ml) was kept at room temperature for 12 h, a 1:1 inclusion crystal of **1** and **8** (**9**) was obtained as colourless prisms (2 g, 86% yield, mp 193-196 C). When **9** was treated with **5a-f** in the presence of a catalytic amount of **4** under the same conditions as for the reaction shown in Table 1 products **10a-f** were obtained in the optical purities shown in Table 2. Optical purities of **10a** and **10d** were relatively higher but those of **10b** and **10c** were lower; whilst in the case of **10e** and **10f**, enantiocontrol was not manifested.



1



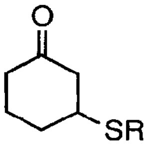
2

$PhCH_2\overset{+}{N}Me_3 \cdot \overset{-}{O}H$

4

RSH

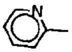
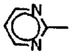
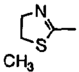
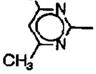
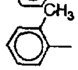
5



6

[†] Chiralpak AS is available from Daicel Chemical Industires, Ltd., Himeji, Japan.

Table 1. Michael addition of **5** to **2** as its inclusion crystal **3** in the presence of a catalytic amount of **4**

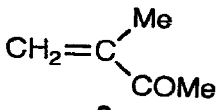
5			product			
	R	reaction time (h)[a]	**6**	yield (%)	optical purity (% ee)[b]	[a]$_D$ (c)[c]
a		24	(+)-**6a**	51	80	+66.0 (0.55)
b		36	(+)-**6b**	58	78	+77.4 (1.0)
c		12	(+)-**6c**	62	---[d]	+10.0 (0.75)
d		36	(+)-**6d**	77	74	+76.4 (0.72)
e		12	rac-**6e**	100	0	0
f		12	rac-**6f**	93	0	0

[a] A mixture of **3**, **5**, and **4** was irradiated by a ultrasound (28 KHz) for 1 h, and was then kept at room temperature. [b] All optical purities were determined by HPLC on the chiral solid phase, Chiralpak AS. [c] All [a]$_D$ values were measured in MeOH except the case of (+)-**6c** ($CHCl_3$). [d] Optical purity was not determined.

Table 2. Michael addition of **5** to **8** as its inclusion crystal **9** in the presence of a catalytic amount of **4**[a]

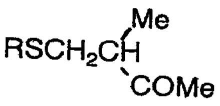
5	product			
	10	yield (%)	optical purity (% ee)[b]	[a]$_D$ (c)[c]
5a	(+)-**10a**	76	49	+35.3 (0.96)
5b	(+)-**10b**	93	9	+5.9 (1.1)
5c	(+)-**10c**	78	53	+4.0 (1.1)
5d	(+)-**10d**	89	4	+4.0 (1.2)
5e	rac-**10e**	63	0	0
5f	rac-**10f**	55	0	0

[a] Reactions were carried out for 23 h by keeping at room temperature after irradiation by ultrasound (28 KHz) for 1 h at room temperature. [b] All optical purities were determined by HPLC on the chiral solid phase, Chiralpak AS. [c] All [a]$_D$ values were measured in MeOH.



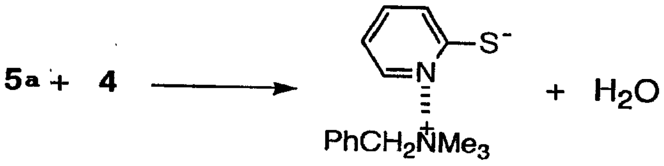
$CH_2{=}C(Me)COMe$

8



$RSCH_2CH(Me)COMe$

10



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Scheme 1

Acknowledgements: We are grateful to the Ministry of Education, Science and Culture, Japanese Government for the Grant-in-Aid for Scientific Research (B) No. 04453102.

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10 Solid state reactions are sometimes accelerated by irradiation with ultrasound, for example. F. Toda, K. Tanaka and S. Iwata, *J. Org. Chem.*, 1989, 54, 3007.
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