Chemistry of Heterocyclic Compounds, Vol. 29, No. 12, 1993

INCLUSION COMPLEXES OF PROCHIRAL HETEROCYCLIC KETONES WITH β-CYCLODEXTRINS AND THEIR REDUCTION WITH SODIUM BOROHYDRIDE

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Alkyl(2-furyl), alkyl(2-thienyl), and methyl pyridyl ketones form stoichiometric inclusion complexes with β-cyclodextrins. Reduction of these complexes in aqueous solution of Na_2CO_3 at room temperature yields the corresponding secondary alcohols with an optical yield which attains 27%.

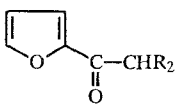
Prochiral furyl-, thienyl-, and pyridyl-containing ketones are the most convenient precursors of the corresponding chiral secondary heterocyclic alcohols. Optically active alkyl furyl, alkyl thienyl, and alkyl pyridyl carbinols have in turn been actively investigated as chiral synthons for asymmetric synthesis [1-8]. We now have the following methods for preparation of optically active furyl and thienyl carbinols: asymmetric reduction of the corresponding ketones (chemical reduction using chirally modified $LiAlH_4$ and $LiBH_4$ [1, 9, 10] or microbiological reduction with baker's yeast [11, 12]), kinetic conversion of racemic alcohols with Sharples reagent [3, 8, 13], enantioselective hydrolysis of heterocyclic alcohol esters [14, 15], and alkylation of furan- and thiophenaldehydes with diethylzinc in the presence of chiral β-amino alcohols as catalysts [16, 17]. Chemical or microbiological asymmetric reduction of acetylpyridines is the basic method of preparation of optically active 1-pyridyl ethanols [7, 11, 18].

Asymmetric reactions of prochiral compounds in a chiral environment in which cyclodextrins (CD) play this role have been actively investigated in the last ten years. CD, cyclic oligosaccharides consisting of six, seven, or eight α-1,4-connected D-glucopyranose rings, form inclusion complexes with very different "guest" molecules [19-21]. The asymmetric effect of the matrix CD has been demonstrated in many reactions of CD complexes of prochiral compounds: halogenation and hydrohalogenation of alkenes [22], hydrocyanation of aldehydes [23], oxidation of sulfides into sulfoxides [24], epoxidation of olefins [25-27], reduction of aromatic ketones [28-33], and Michael addition [34]. The reactions were conducted in heterogeneous conditions with crystalline CD complexes or in homogeneous solutions.

Synthesis of β-cyclodextrin complexes with alkyl hetaryl ketones and their reduction with sodium borohydride were examined in the present study. To the best of our knowledge, there are no published data on the reaction of heterocyclic ketones with CD.

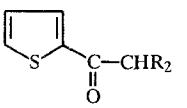
CD complexes with heterocyclic ketones were synthesized with the method in [19-21], which consists of addition of a "guest" to a saturated aqueous solution of a "host," in this case β-CD.

Ketones Ib-e, g-j were prepared by alkylation of the corresponding heterocycles with alkyl halides in conditions of interfacial catalysis [35].



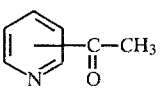
Ia-e

Ia R = H, b R = CH_3, c R = CH_2CH_3, d R = $CH_2CH_2CH_3$, e R = CH_2Ph



I f-j

If R = H, g R = CH_3, h R = CH_2CH_3, i R = $CH_2CH_2CH_3$, j R = CH_2Ph



I k-m

Ik R = 2-pyridyl, l R = 3-pyridyl, m R = 4-pyridyl

Latvian Institute of Organic Synthesis, Riga LV-1006. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1621-1627, December, 1993. Original article submitted October 6, 1993.

0009-3122/93/2912-1399$12.50

TABLE 1. Synthesis of Complexes of Heterocyclic Ketones with β-CD (1:1 Composition)

Ketone	Empirical formula of the complex	Reaction time, h	Yield, %	Ketone	Empirical formula of the complex	Reaction time, h	Yield, %
Ib	$C_{50}H_{80}O_{37}\cdot H_2O$	48	33	Ih	$C_{52}H_{84}O_{36}S\cdot 3H_2O$	48	76
Ic	$C_{52}H_{84}O_{37}\cdot 2H_2O$	72	64	Ii	$C_{54}H_{88}O_{36}S\cdot H_2O$	72	78
Id	$C_{54}H_{88}O_{37}\cdot 2H_2O$	72	74	Ij	$C_{62}H_{88}O_{36}S\cdot H_2O$	48	81
Ie	$C_{68}H_{88}O_{37}$	48	76	Il	$C_{49}H_{77}NO_{36}\cdot 6H_2O$	12	99
If	$C_{48}H_{76}O_{36}S$	48	50	Im	$C_{49}H_{77}NO_{36}\cdot 6H_2O$	12	99
Ig	$C_{50}H_{80}O_{36}S\cdot 2H_2O$	72	82				

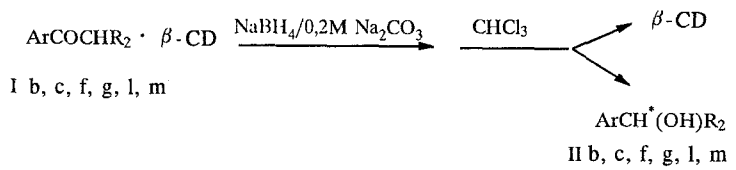
On addition of liquid, water-immiscible alkyl (2-furyl) (Ib-d) and alkyl (2-thienyl) ketones (If-i) to a saturated aqueous solution of β-cyclodextrin, a complex which precipitates into sediment is gradually formed. In the case of solid ketones Ie and Ij, organic molecules are also drawn into the solution with subsequent precipitation of the inclusion complex formed into the sediment.

A complex is not formed only in the case of 2-acetylfuran (Ia). The solubility of the complex formed decreases and its preparative yield correspondingly increases as the lyophilicity of the alkyl substituent increases (Table 1).

The solubility of the β-cyclodextrin complexes with acetylpyridines is much higher than for complexes with furan- and thiophene-containing ketones. For this reason, the acetylpyridine complexes were synthesized by another method. A stoichiometric amount of ketone (Ik-m) was added to a warm (35-40°C) saturated aqueous solution of β-CD and the mixture was left at room temperature for 12 h. The water was then evaporated at reduced pressure. Ketones Il, m formed inclusion complexes with β-CD with a quantitative yield; no complex formed in the case of 2-acetylpyridine (Ik). The data from elemental analysis and PMR spectroscopy (with the ratio of the intensities of the signals from "guest" and "host" protons) suggest that heterocyclic ketones form complexes with β-cyclodextrin in the ratio of 1:1.

Significant shifts of the proton signals of the cyclodextrin matrix are observed in the PMR spectra recorded in D_2O for complexes highly soluble in water (Table 1), which clearly indicates complexation [36]. A comparison of the PMR spectra of individual ketones Ib, f, l, m with the spectra of their CD complexes also indicates the existence of complexation, since the signals of all protons of the "guest" molecule are shifted to strong fields by 0.07-0.14 ppm (see Table 2). Such a comparison is not possible for the other ketones due to their insolubility in water.

For obtaining optically active hetaryl carbinols, the synthesized complexes of alkyl hetaryl ketones Ib-j, l, m were reduced with sodium borohydride in 0.2 M aqueous solution of Na_2CO_3. Preliminary experiments showed that the ketones bound in the complex reduced much more slowly than free ketones. This could be determined by both the decrease in the reactivity due to complexation and by steric hindrances and the low solubility of the complexes (the latter is characteristic of furan- and thiophene-containing compounds — reactions take place for them in almost heterogeneous conditions). Ketones Id, e, h-j could not be reduced. Complexes of the remaining ketones slowly (2-8 days) reduced, so that the corresponding alkyl hetaryl carbinols IIb, c, f, g, l, m were obtained as a result.



Ar = 2-furyl-, 2-thienyl-, 3- and 4-pyridyl; R = H, CH_3, CH_2CH_3.

The products of reduction separated with a preparative yield of 41-100% exhibited optical activity. The optical purity and absolute configuration of the carbinols obtained were determined by comparison with the values and optical rotation signs of pure enantiomers (Table 3). For comparison, the enantiomeric excess in the case of furan- and thiophene-containing alcohols was also determined by quantitative GLC and GLC-MS analysis of diastereomeric esters prepared by the reaction of the corresponding carbinols and camphanic acid esters (see Table 3). The analysis of these data showed that asymmetric induction increases with an increase in the bulk of the alkyl substituent. The optical yield attains the maximum (27%) in the case of IIg.

TABLE 2. PMR Spectra of Heterocyclic Ketones and Their Complexes with β-Cyclodextrin (360 MHz, D_2O/DSS

Compound	Chemical shifts of "guest" protons						Chemical shifts of "host" protons				
	H_2	H_4	H_5	CH	CH_2	CH_3	H_1	H_2	H3	H_4	H_5+6-CH_2
Ib ·β-CD	7,404	6,603	7,730	3,331	—	1,081	4,956	3,538	3,827	3,476	3,690
Ib	7,538	6,692	7,820	3,451	—	1,172	—	—	—	—	—
Ib ·β-CD	7,508	6,654	7,792	3,108	1,577	0,788	4,999	3,580	3,867	3,517	3,730
If ·β-CD	7,836	7,181	7,881	—	—	2,556	4,986	3,565	3,852	3,505	3,730
If	7,908	7,252	7,962	—	—	2,630	—	—	—	—	—
Ig ·β-CD	7,862	7,209	7,903	—*	—	1,153	4,994	3,574	3,856	3,514	3,710
Ih ·β-CD	7,926	7,249	7,979	3,302	1,642	0,835	5,030	3,611	3,889	3,552	3,750
	H_2	H_3	H_4	H_5	H_6	CH_3					
Im ·β-CD	8,944	—	8,237	7,480	8,611	2,562	4,928	3,513	3,735	3,444	3,610
Im	9,076	—	8,372	7,601	8,728	2,693	—	—	—	—	—
Im ·β-CD	8,619	7,740	—	7,740	8,619	2,560	4,927	3,511	3,735	3,442	3,600
Im	8,730	7,856	—	7,856	8,730	2,690	—	—	—	—	—
β-CD	—	—	—	—	—	—	4,928	3,508	3,804	3,446	3,690

*Signal overlapped by the signal of β-CD protons.

TABLE 3. Asymmetric Reduction of β-CD Complexes of Aryl Hetaryl Ketones with Sodium Borohydride (25°C, ketone·β-CD:$NaBH_4$ molar ratio, 1:2)

Initial complex	Reaction time, days	Carbinol	Yield, %	$[\alpha]_D^{25}$	Optical purity, %*	Configuration	Enantiomeric excess, %*2
Ib·β-CD	8	IIb	41	−0,69 (c=11,6, $CHCl_3$)	4,0	S	1
Ic·β-CD	2	IIc	61	−4,28 (c=7,7, $CHCl_3$)	—	*3	13
If·β-CD	2	IIf	77	−1,75 (c=9,1, $CHCl_3$)	7,5	S	6
Ig·β-CD	7	IIg	42	−5,35 (c=8,2, $CHCl_3$)	34,0	S	27
Il·β-CD	2	IIl	100	+8,00 (c=2,0, MeOH)	20,0	R	*3
Im·β-CD	2	IIm	100	+2,50 (c=2,0, EtOH)	6,0	R	*3

*Calculated based on the maximum optical rotation: (R)-(+)-(IIb): $[\alpha]_D^{25}$ + 18.1 (>95%) (c = 1.04, $CHCl_3$) [3]; (S)-(-)-(IIf): $[\alpha]_D^{25}$ −23.3 (100%) c = 1.5, $CHCl_3$) [37]; (R)-(+)-(IIg): $[\alpha]_D^{25}$ +14.2 (91%) (c = 1.02, $CHCl_3$) [13]; (R)-(+)-(IIl): $[\alpha]_D^{25}$ +40.2 (100%) (c = 0.87, MeOH) [38]; (R)-(+)-(IIm): $[\alpha]_D^{25}$ +46.7 (100%) (c = 0.51, EtOH) [18].

*2 Calculated with the results of GLC and GLC/MS analyses of the corresponding diastereomeric camphanic acid esters.

*3 Not determined.

Complexes of 3- and 4-acetylpyridines with modified β-CD — heptakis(2,6-di-O-methyl)- and heptakis(2,3,6-tri-O-methyl)-β-cyclodextrins — were prepared for evaluating the effect of the CD matrix. The cyclodextrins were synthesized by partial or total methylation of β-CD with the method in [39]. Complexes of 1:1 composition (according to the data from the PMR spectra) were prepared similar to the complexes with unmethylated β-CD. The experiments showed that reduction of complexes of acetylpyridines with methylated CD yields racemic 1-pyridylethanols. The presence of free OH groups in the matrix is thus a necessary condition for asymmetric induction. The study showed that prochiral alkyl hetaryl ketones form stoichiometric inclusion complexes with β-cyclodextrin. Reduction of these complexes yields the corresponding secondary alcohols with an optical yield of up to 27% [40].

EXPERIMENTAL

The PMR spectra were recorded on a Bruker WM-360 spectrometer at 360 MHz in D_2O or $CDCl_3$ using DSS or TMS as the internal standard. The mass spectra were recorded on a MS-25 (Kratos) chromatograph−mass spectrometer with an ionizing electron energy of 70 eV. GLC analysis was conducted on a Chrom-5 chromatograph with a flame-ionization detector and glass column [2.4 m × 3 mm packed with 10% SE-30 + 2.5% Reoplex 400/Chromosorb W-AW (60-80 mesh) for determination of furyl- and thienyl-containing derivatives, and 1.2 m × 3 mm packed with 5% OV-17/Chromosorb W-HP (80-100 mesh) for pyridyl-containing derivatives]. Helium was the carrier gas (60 ml/min). The temperature of the analysis varied within 150-180°C as a function of the composition of the reaction mixture. The GLC analysis of alkyl hetaryl carbinol and camphanic acid diastereomeric esters was conducted on a Hewlett-Packard (model 5890) chromatograph with a HP-1 quartz capillary column (5 m × 0.53 mm) with linear temperature programming from 100 to 200°C at the rate of 4°C/min. Helium was the carrier gas. The angle of optical rotation was determined on Autopol 2 (Rudolf Research) and Polamat A (Carl Zeiss) polarimeters.

β-Cyclodextrin (Reanal), (1S)-(-)-camphanic acid chloride, 2-acetylthiophene, and sodium borohydride (Fluka) were used without additional purification. Acetylpyridines (Fluka) and 2-acetylfuran (Reakhim) were vacuum distilled before use. Alkyl(2-furyl) and alkyl-(2-thienyl) ketones were prepared by the method described in [35].

Synthesis of Complexes of Alkyl Furyl (Ia-e) and Alkyl Thienyl Ketones (If-j) with β-cyclodextrin (General Method). An equimolar amount of the corresponding ketone was added to a saturated solution of β-Cyclodextrin in water at room temperature and mixed for 48-72 h. The precipitated sediment was filtered off and dried first in air and then in a desiccator over P_2O_5. The yields of the complexes, data from elemental analysis, and PMR spectra are reported in Tables 1 and 2.

Synthesis of Complexes of Acetylpyridines (Il, m) with β-Cyclodextrins (General Method). β-Cyclodextrin (4.54 g, 4 mmoles) was dissolved in 230 ml of warm (35-40°C) distilled water. The corresponding acetylpyridine (0.484 g, 4 mmoles) was added to the transparent solution obtained and left overnight. The water was then evaporated in a rotary evaporator, and the white powder obtained was dried in a desiccator over P_2O_5, yielding 5 g (99%) of the complex Il,m × β-CD. The data on the conditions of synthesis, PMR spectra, and elemental analysis are reported in Tables 1 and 2.

Reduction of β-Cyclodextrin Complexes of Alkyl Hetaryl Ketones with Sodium Borohydride (General Method on the Example of Reduction of Ic·β-CD Complex). $NaBH_4$ (0.53 g, 13.84 mmoles) was added to a suspension of Ic·β-CD complex (9 g, 6.92 mmoles) in 0.2 M aqueous solution of Na_2CO_3 (35 ml), and the mixture obtained was stirred for 48 h at room temperature. The evolution of the reaction was monitored by GLC and GLC–MS analysis. At the end of the reaction, the mixture was extracted with chloroform (3 × 100 ml). The organic layer was dried over $MgSO_4$, filtered, and the solvent was eliminated at reduced pressure. Vacuum distillation of the residue yielded 0.71 g (yield of 61%) of 1-(2-furyl)-2-ethyl-1-butanol (IIc). PMR ($CDCl_3$) δ: 0.84 (6H, m, $CH(CH_2CH_3)_2$); 1.1-1.8 (5H, m, $CH(CH_2CH_3)_2$); 1.89 (1H, br. s, OH); 4.60 (1H, d, J = 6 Hz, CHOH); 6.15 (1H, d.d, J_1 = 0.8 Hz, J_2 = 3.1 Hz, 3-H); 6.27 (1H, d.d, J_1 = 1.8 Hz, J_2 = 3.1 Hz, 4-H); 7.29 (1H, d.d, J_1 = 0.8 Hz, J_2 = 1.8 Hz, 5-H). Elemental analysis: calculated for $C_{16}H_{16}O_2$: C 71.39; H 9.59; found: C 70.94; H 9.63. Mass spectrum, *m/z*: 168 (M^+, 3), 97 (M^+-$CHEt_2$, 100), 69 (4), 55 (5), 41 (16). The reaction time, optical rotation, and optical purity are reported in Table 3.

Determination of the Enantiomeric Excess of Alkyl Furyl and Alkyl Thienyl Carbinols (IIb, c, f, g) (General Method on the Example of IIc). Here 23.1 mg (0.137 mmole) of IIc, 0.15 g (0.867 mmole) of (1S)-(-)-camphanic acid chloride, and 0.056 ml (0.687 mmole) of pyridine were dissolved in dry benzene and stirred at room temperature for 3 h. At the end of the reaction (GLC monitoring), the ratio of diastereomeric esters was determined in a capillary column by GLC and also, for comparison, by GLC–MS analysis. The enantiomeric excess of the predominant optical isomer was calculated as a result of both analyses, which produced very close values (see Table 3).

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