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Communication

Inclusion-dependent mechanism of modification of cyclodextrins with heterocycles

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Abstract: Mono(6-deoxy-dimethylpyridinium)-β-cyclodextrins have been synthesized in reaction of mono (p-toluenesulfonyl) derivative of β–cyclodextrin with the appropriate lutidine under microwave irradiation and conventional conditions. The results indicate that the mechanism consists of inclusion complex formation.

Keywords: Monomodified cyclodextrin, lutidines, microwave irradiation

1 Introduction

Cyclodextrins (CD) as well as their derivatives and polymers have gained high popularity in the last years because of their industrial importance [1-3]. Their abilities to complex a wide variety of organic and inorganic compounds are broadly utilized. CD derivatives may form chemoreceptors for different guests [4,5]. Interestingly, similar structures could be used as carriers to increase bioavailability of water insoluble drugs [6,7]. Many new possibilities have been discovered with new, microwave-assisted protocols for synthesis of such structures [8-11]. This prompted us to present our preliminary observations regarding to new procedure facilitating synthesis of new monomodified, water soluble β–CD derivatives, containing heterocyclic moieties. These could be of great importance in understanding the reactivities of cyclodextrins under both conventional and solid state,

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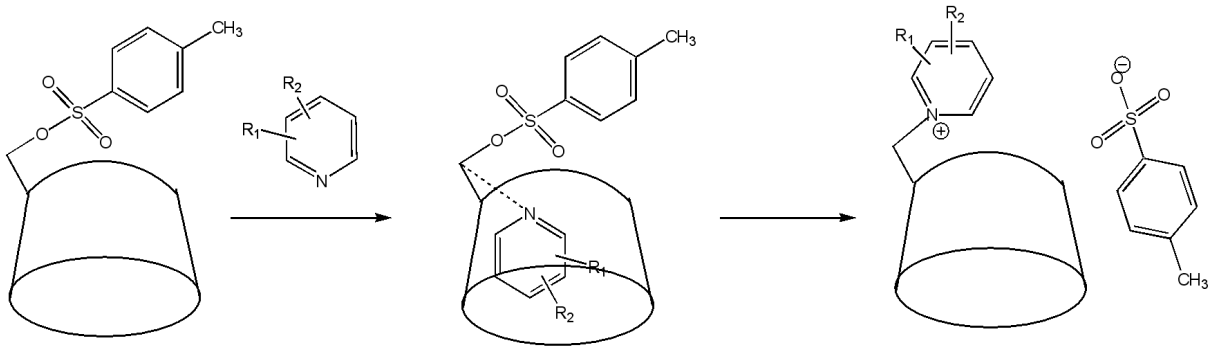
microwave assisted conditions [12].

2 Results and discussion

In our experience, an efficient way of obtaining water soluble monofunctionalized cyclodextrins is through the formation of monotosyl derivatives. There are a number of methods of monotosylation of CDs [13,14]. We performed this using simple and easy to monitor protocol [12]. We synthesized p-toluenesulfonyl salts of β-cyclodextrin functionalized with dimethylpyridine moieties as shown in Scheme 1. The microwave-assisted synthesis affords lower yields than conventional heating; however, this technique is much faster and very convenient. Table 1 shows the results obtained by conventional and microwave-assisted synthesis in comparison to similar compounds described in the literature.



Scheme 1 Synthesis of monomodified of β–CD.

Products obtained this way need no further purification by column chromatography. Use of equimolar amounts of substrates reduces the waste and additional chemicals necessary in synthesis (e.g. solvents). Microwave-assisted synthesis in solid state reported here matches well with the aims of "green chemistry".

Unexpectedly, we observed that there was no product in the cases of 2,6-dimethylpyridine, 3,5-dimethylpyridine, and 2,4,6-collidine. An explanation of this observation may be an effect of steric disturbances during the formation of inclusion complexes, as shown in Scheme 2. This implicates that these reactions are undergoing a two-step mechanism. First, the molecule of substituted pyridine is complexed into the β-CD cavity, then the proper substitution takes place. In cases of structurally extended compounds the inclusion complex is formed in the "tail first" manner that prevents the next step and product formation.

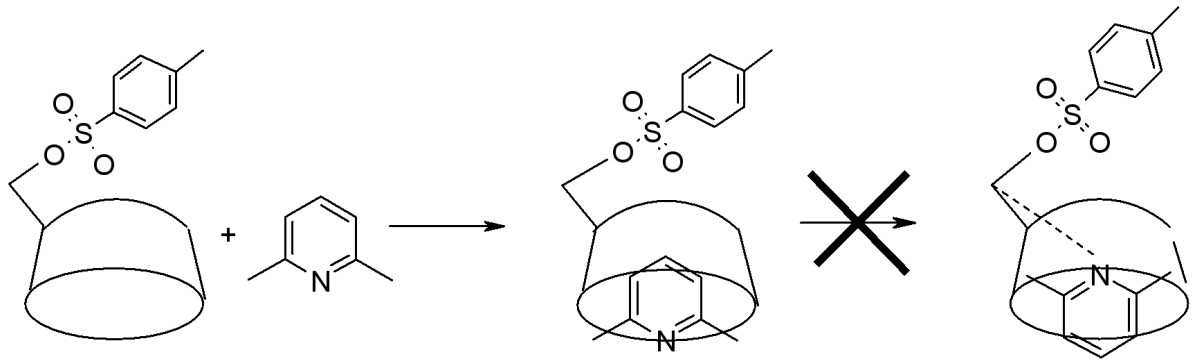
3 Experimental section

All ^{1}H NMR and 2D NMR spectra were recorded on Bruker NMR 300 MHz instrument in DMSO-d6; diffuse signals from easily exchangeable protons were not listed. For

Compound	Procedure	
	Microwave	Conventional
Pyridine	–	12h/18 % [15]
3-methyl-pyridine	–	12h/91 % [12]
4-methyl-pyridine	–	12h/89 % [12]
2,3-dimethyl-pyridine	2min/47 %	2h/90 %
2,4-dimethyl-pyridine	2min/65 %	2h/93.5 %
3,4-dimethyl-pyridine	2min/65 %	2h/94 %
2,6-dimethyl-pyridine	–	–*
3,5-dimethyl-pyridine	–	–*
2,4,6-trimethyl-pyridine	–	–*

* After 12h reflux or 2min irradiation the product was not formed.

Table 1 Traditional and microwave assisted synthesis of mono[6–(lutidinyl)–6–deoxy]–β–cyclodextrins



Scheme 2 Inclusion complex dependent mechanism of modification of β–CD

better visualization, examples of ^{1}HNMR and 2D NMR (in COSY experiment) spectra of mono(6-deoxy-6-(2,3-dimethyl)pyridinium)-β-cyclodextrin tosylate are shown in Supporting Information (www.cesj.com/chemistry/files/13-paper-Support-SI1-SI3.pdf). Traditional reactions were carried out in a standard oil bath and microwave assisted synthesis were carried out using a Sharp domestic microwave oven. IR spectra were recorded on a Nexus Nicloet FTIR apparatus (KBr). TLC experiments were done on SiO_2 precoated plates with UV indicator (butanol/ethanol/water in proportions 3/5/3 was used as a mobile phase).

3.1 Materials

For the reason that β–cyclodextrin forms very stable complex with six molecules of water [2], β-CD, after recrystallization from water was dried under low pressure for 12 hours at 100 °C. Pyridine was dried with solid NaOH and then fractionally distilled. Commercially

available p–toluenesulfonyl chloride (Anal. purity) and pyridine derivatives were used without further purification.

MTs–β–CD was synthesized as described before [8]. Crude MTs–β–CD was recrystallized from water and dried under low pressure at 90 °C. Monomodification was verified by liquid chromatography followed by ^{1}H NMR spectroscopy, yield 5 g, 22 % [12].

3.2 General procedure A

0.5 g of MTs–β–CD was added into 30 ml of lutidine and the solution was refluxed under nitrogen atmosphere for 2 hours. Next the precipitate was extracted with acetone in a Soxhlet apparatus, dissolved in a small amount of water and after filtering, precipitated with acetone and centrifuged, filtered and dried under vacuum at 60 °C. When it was necessary the product was purified by column chromatography on Sephadex G25.

3.3 General procedure B

0.5 g of MTs–β–CD and 3 ml of lutidine were mixed with 5 g of Al_2O_3 Montmorillonite and put into the open reactor. Then the mixture was subjected to microwave irradiation for 2 minutes (4 x 0.5 minutes with 2-minute intervals) at output power level 850 W. After the reaction the mixture was added to a small amount of water, filtered and the product precipitated with an excess of acetone. Next the precipitate was centrifuged and dried under vacuum at 60 °C.

Mono(6-deoxy-6-(2,3-dimethyl)pyridinium)-β-cyclodextrin tosylate, was obtained as a light brown solid.
^{1}HNMR (DMSO-d6) (δ ppm) 2.082(s, 3H); 2.286(s, 3H); 2.497(s, 3H); 3.20–5.12(m, 42H); 6.28(s 7H); 7.10(d, J=7.8Hz 2H). IR(neat, cm^{-1}); 3374, 2928, 1646, 1558, 1417, 1367, 1300, 1156, 1080, 1032, 950–530.

Mono(6-deoxy-6-(2,4-dimethyl)pyridinium)-β-cyclodextrin tosylate, was obtained as a light brown solid.
^{1}HNMR (DMSO-d6) (δ ppm) 2.25 (s, 3H); 2.375 (s, 3H); 2.475 (s, 3H); 2.875-5.125 (m, 42H); 5.75 (s, 7H); 7.075 (d, J=7.5Hz, 2H); 7.475 (d, J=7.5Hz, 2H); 7.69-7.95 (m, 1H); 8.25 (d, J=6.25Hz, 1H); 8.65-8.875 (m, 1H). IR(neat, cm^{-1}); 3374, 2928, 1643, 1573, 1412, 1367, 1300, 1156, 1080, 1031, 950–530.

Mono(6-deoxy-6-(3,4-dimethyl)pyridinium)-β-cyclodextrin tosylate, was obtained as the yellow solid.
^{1}HNMR (DMSO-d6) (δ ppm) 2.079 (s, 3H); 2.29 (s, 3H); 2.5 (s, 3H); 2.9-5.1 (m, 42H); 5.76 (s, 7H); 7.14 (d, J=7.8Hz, 2H); 7.5 (d, J=8.3Hz, 2H); 7.76-8.1 (m, 1H); 8.16-8.37 (m, 1H); 8.52-8.9 (m, 1H). IR (neat, cm^{-1}); 3374, 2928, 1642, 1576, 1412, 1367, 1300, 1156, 1080, 1032, 950–530.

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