9th International Electronic Conference on Synthetic Organic Chemistry. ECSOC-9
1-30 November 2005. http://www.usc.es/congresos/ecsoc/9/ECSOC9.HTM & http://www.mdpi.net/ecsoc/

Monomodification of cyclodextrins with pyridine derivatives. Inclusion dependent mechanism.

[E004]

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Introduction

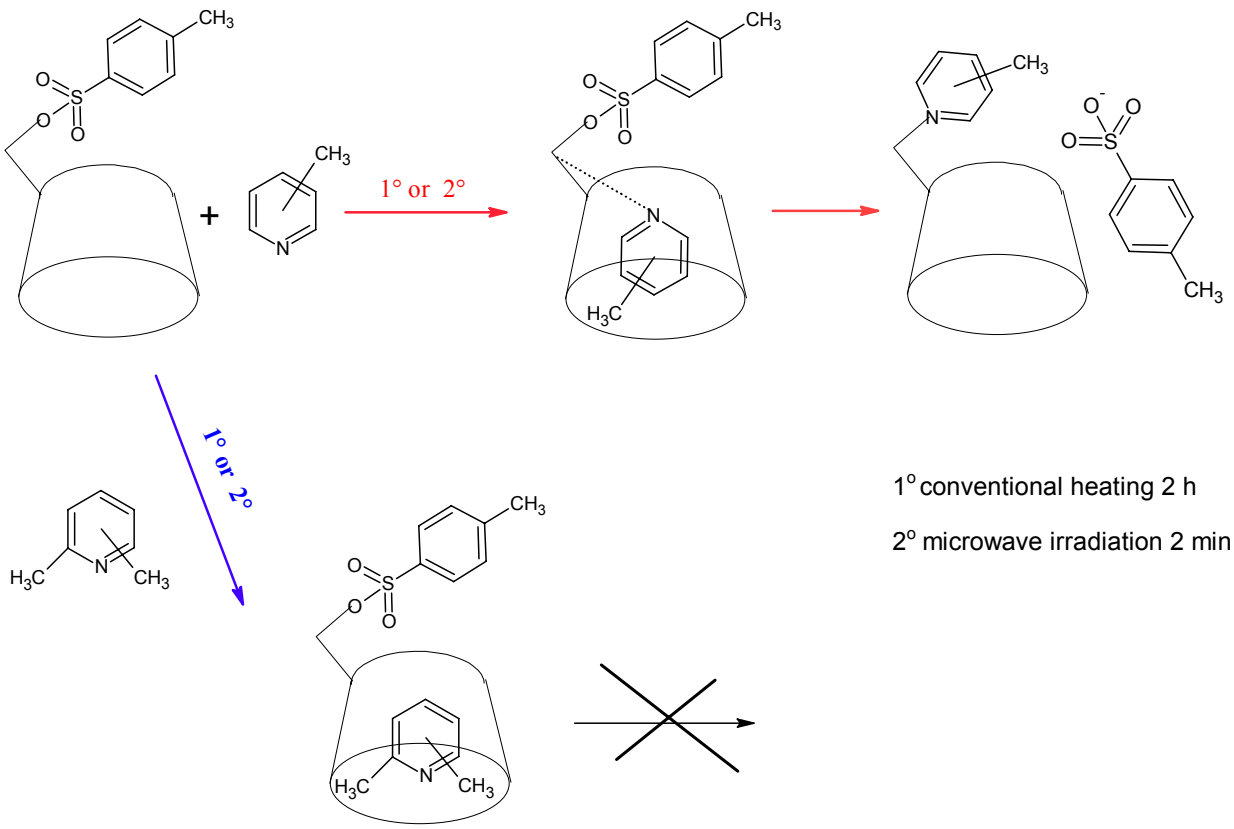
Main advantage of cyclodextrins relates to their ability to formation of strong complexes with wide variety of molecules. Thus CD derivatives may form chemoreceptors for different guests [1, 2]. Interestingly similar structures could be used as carriers to increase bioavability of water insoluble drugs [3, 4]. These possibilities are greatly facilitated by modification of CDs trunk with different substituents. Many new possibilities have been discovered with new, microwave assisted protocols of synthesis such structures [5-8]. In our study on supramolecular recognition system and water soluble modified cyclodextrins we explored some ways leading to CD derivatives modified with pyridine moiety [9, 10]. During these works we obtain some unexpected results that indicates mechanism of such derivatisation [11, 12].

This prompted us to present our preliminary observations regarding to new procedure facilitating synthesis of new monomodified, water soluble β–CD derivatives, containing heterocyclic moiety.

Results and discussion

In our experience, efficient way of obtaining soluble in water monofunctionalized cyclodextrins leads through the formation of monotosyl derivative. We synthesized p-toluenesulfonyl salts of β-cyclodextrin functionalized with

dimethylpyridine moiety as shown in scheme 1 (red path). The microwave assisted synthesis affords in lower yield than thermal, however this technique is much faster and very convenient. Table 1 shows the results obtained by thermal and microwave assisted synthesis in comparison to similar compounds described in literature.



Scheme 1 Inclusion complex dependent mechanism of modification of β-CD

Product obtained this way needs no further purification by column chromatography. Use of equimolar amounts of substrates reduces the waste and additional chemicals necessary in synthesis (e.g. solvents).

Compound	Procedure	
	Microwave	Conventional
Pyridine	–	12h/18%[13]
3-methyl-pyridine	–	12h/91%[14]
4-methyl-pyridine	–	12h/89%[14]
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 refluxed during 12h or irradiated during 2min the product was not formed.

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

Surprisingly no product in case 2,6-dimethylpyridine, 3,5-dimethylpyridine, and 2,4,6-collidine was observed. This is probably due to an effect of spatial disturbances during the formation of inclusion complex, as shown in scheme 1 (blue path). This implicates that these reactions are undergoing according to two step mechanism. First the molecule of pyridine derivative is complexed into the β-CD cavity, then the proper substitution takes place. In case of structurally extended compounds the inclusion complex is formed in the "tail first" manner that prevents the next step and product formation.

Experimental section

MTs–β–CD was synthesized as described before [5]. 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% [14].

Substitution with pyridine derivatives were performed as described before [11]. Further studies performed on wide group of compounds will help to understand all aspects of the mechanism.

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