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Greening the esterification between isosorbide and acetic acid

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ABSTRACT

This contribution deals with the investigation of greener conditions for the preparation of 2,5-diacetyl-isosorbide from the bio-based substances isosorbide and acetic acid. The influence of solvent, catalyst and reactant ratio on the course of the isosorbide conversion and selectivity to 2,5-diacetyl-isosorbide as well as to the intermediate 2-acetyl-isosorbide is examined. It was found that the conventionally used solvent toluene can be substituted by the greener solvent n-propyl acetate. Additionally, the homogeneous acid catalyst p-toluene sulfonic acid can be replaced by the heterogeneous catalyst Amberlyst-15, resulting in an easier isolation of the desired 2,5-diacetyl-isosorbide, this being an important precursor for the vasodilatory drug isosorbide-5-nitrate.

1. Introduction

The optimisation of production routes for pharmaceuticals under a green chemistry perspective is a contribution towards a more sustainable chemical/pharmaceutical industry (Kümmerer and Hempel, 2010). In order to lower the risk of a future feedstock supply shortfall, all reactants have to be obtained from renewable (bio-based) feedstocks. This is particularly important for pharmaceuticals which help to prevent or cure life-threatening diseases and which will therefore still be urgently needed even in a sustainable, i.e. eco sufficiency-based economy (Princen, 2005; Paech, 2012).

Isosorbide (2,4-3,6-dianhydro-D-sorbitol) is a bio-based diol which has potential as a future platform molecule for the production of bio-based pharmaceuticals, solvents and polymers (Rose and Palkovits, 2012; Farmer and Mascal, 2015).

The esterification of isosorbide with acetic acid is of importance for the pharmaceutical industry because 2-acetyl-isosorbide is the intermediate for the production of isosorbide-5-nitrate, which is the active pharmaceutical ingredient in vasodilatory drugs like Isomonit, Imdur, Monoket or Chemydur used for the treatment of angina pectoris and coronary artery disease (PubChem, 2017; Tan et al., 2013). Isosorbide-2,5-dinitrate is a vasodilatory drug, too, but the active metabolite is the mononitrate, so that the dinitrate brings effectively too much nitrate into the body which can cause insensitivity towards such drugs. Furthermore the metabolisation of isosorbide-2,5-dinitrate is much faster than for isosorbide-5-nitrate which forces the patient to take the drug twice instead of only once a day causing difficulties for some patients (Lehman, 2010; Gunasekara and Noble, 1999). Thus, from a pharmaceutical point of view, the use of isosorbide-5-nitrate is preferred over the dinitrated equivalent.

Fig. 1 shows a possible synthesis pathway from isosorbide to isosorbide-5-nitrate as described by Karl Schönafinger in two German patents from 1982 (Schönafinger, 1982a, 1982b). In a first step isosorbide is reacted with acetic acid in the presence of p-toluene sulfonic acid (p-TSA) as the acidic catalyst. Toluene is used as the hetero-azeotropic solvent for water removal in a Dean-Stark apparatus. 2-acetyl-isosorbide is then isolated and nitrated, with the 2-acetyl group protecting the former 2-hydroxyl group from nitration. The final synthesis step is the hydrolysis of the 2-acetyl group to give isosorbide-5-nitrate in a yield of over 60% in respect to the isosorbide starting material.

It was found that the isolation of the mono-acetylated intermediate 2-acetyl-isosorbide is more difficult than the isolation of the di-acetylated product 2,5-diacetyl-isosorbide, because the synthesis mixture contains unreacted isosorbide, 5-acetyl-isosorbide and 2,5-diacetyl-isosorbide, too, if full acetylation is avoided. The results of the present study (see Table 1) indicate that a maximum theoretical yield of 2-acetyl-isosorbide of 38% can be obtained before further acetylation to 2,5-diacetyl-isosorbide takes place. To increase the 2-acetyl-isosorbide yield, the patent (Schönafinger, 1982a) suggests a simple two-step process, where the first step is the complete esterification of isosorbide to form 2,5-diacetyl-isosorbide (conversion ca. 90%). In a second step 2,5-diacetyl-isosorbide is converted back into 2-acetyl-isosorbide via a short treatment with KOH or p-TSA at higher temperature, which is reported to yield 84% (only step 2) or 76% (steps 1 + 2) 2-acetyl-isosorbide with only minor impurities of isosorbide and 5-acetyl-isosorbide. An alternative, enzymatic route converts 2,5-diacetyl-isosorbide with similarly high selectivity to 2-acetyl-isosorbide or 5-acetyl-

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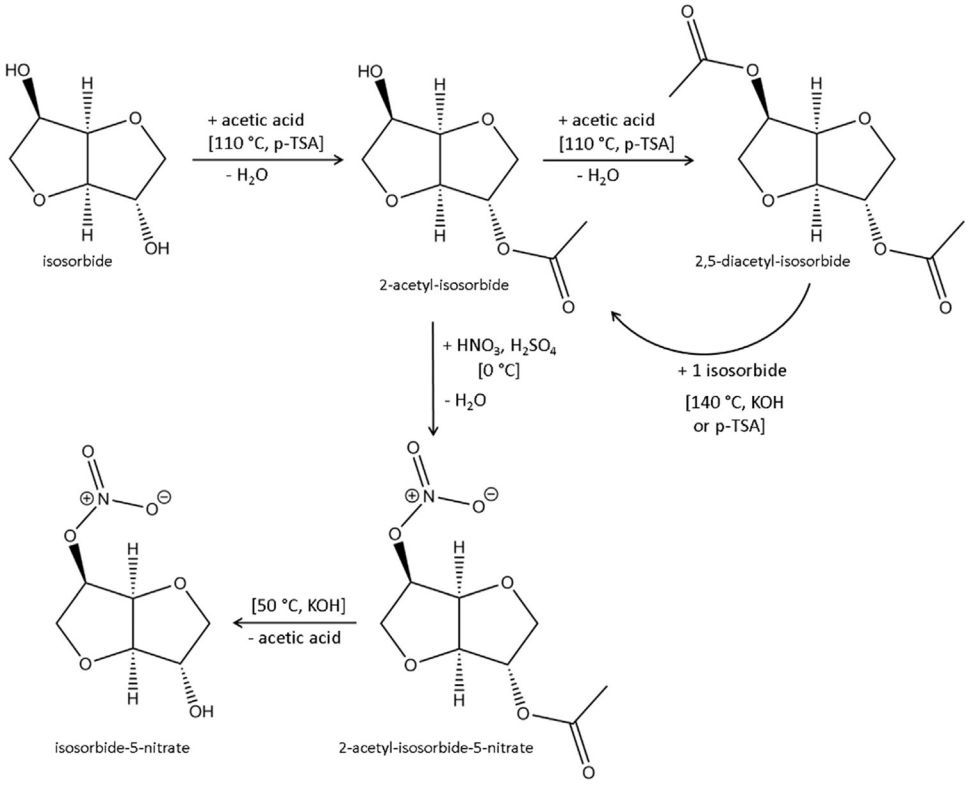

Fig. 1. Synthesis route for the production of isosorbide-5-nitrate via the esterification of isosorbide with acetic acid according to Schönafinger (1982a, 1982b).

Table 1
Synthesis variations undertaken in this study; for each experiment 10 g (0.069 mol) isosorbide and 40 ml solvent were used; the maximum mol fractions of 2,5-diacetyl-isosorbide (2,5-DAI) and 2-acetyl-isosorbide (2-AI) observed during the syntheses were calculated according to Eq. (1); the numbers in the "image" column relate to photographs of the final synthesis mixtures which can be found in the Supplementary information in Fig. S6.

Variation	Acetic acid	Catalyst	Solvent	T [°C]	Image	Max. mol fraction (after synthesis time)	
						2-AI	2,5-DAI
Standard synthesis	15 ml (0.25 mol)	0.25 g Amberlyst-15	Toluene	111	1	0.33 (3 h)	0.99 (30 h)
Acetic acid amount	12 ml (0.20 mol)	0.25 g Amberlyst-15	Toluene	111		0.36 (6 h)	0.68 (31 h)
	9 ml (0.15 mol)				2	0.38 (6 h)	0.58 (30 h)
	6 ml (0.10 mol)				3	0.38 (6 h)	0.29 (30 h)
Catalyst amount	15 ml (0.25 mol)	0.50 g Amberlyst-15	Toluene	111		0.30 (1 h)	0.91 (25 h)
		0.15 g Amberlyst-15			4	0.34 (5 h)	0.79 (30 h)
		0.05 g Amberlyst-15			5	0.37 (3 h)	0.61 (26 h)
Type of catalyst	15 ml (0.25 mol)	0.5 g H-Y	Toluene	111		0.33 (23 h)	0.10 (28 h)
		0.5 g H-ZSM5				0.32 (55 h)	0.28 (79 h)
		0.5 g hydrotalcite				0.30 (54 h)	0.20 (54 h)
		0.4 g p-TSA (mono hydrate)				0.34 (2 h)	0.99 (26 h)
		0.02 g H_2SO_4				0.32 (4 h)	0.99 (26 h)
		No catalyst				0.31 (50 h)	0.45 (120)
Type of solvent	15 ml (0.25 mol)	0.25 g Amberlyst-15	Toluene	111	7	0.33 (3 h)	0.88 (25 h)
			N-propyl acetate	102	6,8	0.31 (5 h)	0.99 (51 h)
			Methylcyclopentane	72		0.28 (6 h)	0.59 (27 h)

isosorbide, respectively (Schneider and Seemayer, 1993).

According to Schönafinger (1982b) the direct nitration of isosorbide to isosorbide-5-nitrate is not preferable because it results in a mixture of different nitrates where isosorbide-5-nitrate is a minor component, thus giving very low yields after costly purification. Also the direct nitration of isosorbide to isosorbide-2,5-dinitrate and subsequent selective reduction to isosorbide-5-nitrate seems inappropriate from a green as well as economic point of view since it involves substances like toxic dichloromethane, high amounts of toxic sodium borohydride (2 M equivalents) and expensive catalysts like iron phthalocyanine (Marston et al., 2001). So there is a need for the intermediate acetylation of isosorbide.

From a life cycle and safety perspective the use of acetic acid instead of acetyl chloride or acetic anhydride (Otera and Nishikido, 2010) is the greener way of acetylating isosorbide. Among the reported synthesis procedures using acetic acid for the esterification of isosorbide (Thiyagarajan et al., 2014; Howard and Sanborn, 2009; Cekovic and Tokic, 1989; Schönafinger, 1982a) the industrially most appropriate and greenest protocol seems to be the one described in example 1 of the patent of Schönafinger (1982a), which was therefore used as the state of the art procedure for our greening study. However, the acid catalyst is p-toluene sulfonic acid (p-TSA), which is homogeneous and thus not reusable, requires neutralisation agents for its removal after synthesis and subsequently leads to the generation of salty waste water as well as the use of toxic CH_2Cl_2 for the extraction of the reaction product (Schönafinger, 1982a). Furthermore, toluene is used as a solvent for the