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Fries rearrangement in methane sulfonic acid, an environmental friendly acid

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Abstract

The Fries rearrangement of phenyl acetate for the paracetamol process is usually performed in hydrofluoric acid (HF). We have optimized this reaction with methane sulfonic acid (MSA), a strong, stable and biodegradable acid, to give *para*-hydroxyacetophenone with high conversion and selectivity (up to 92% of *para*-isomer and 8% of *ortho*-isomer at 100% conversion). © 2002 Elsevier Science B.V. All rights reserved.

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1. Introduction

In the production of industrial pharmaceuticals, dyes and agrochemicals, the selective Fries rearrangement of esters of aromatic alcohols serves as valuable synthesis step [1–5]. For example, the first step of the Hoechst Celanese manufacturing process of paracetamol **1**, the well known analgesic drug, is the Fries rearrangement of phenyl acetate **2** in *para*-hydroxyacetophenone **3a** [1] (Scheme 1).

Classical Fries rearrangement are generally catalyzed by acids like hydrofluoric acid (HF) [1,8], the most frequently used, $AlCl_3$ [6,8], BF_3 [7,8], $TiCl_4$ [5] or $SnCl_4$ [5]. However, HF which acts as catalyst and solvent is very toxic, corrosive, volatile (b.p. 15 °C) and gives necroses. Aluminum trichloride is also corrosive and reacts violently with water. Boron trifluoride is very toxic, corrosive and gives a strong reaction with water. Furthermore, the reaction mixture has to undergo a hydrolysis step generating corrosive gases and contaminated salts. In this step, these homogeneous catalysts are destroyed and cannot be recycled.

In the case of the Fries rearrangement of phenyl acetate into *para*-hydroxyacetophenone, a paracetamol intermediate, different acids have been already evaluated:

- currently used liquid (HF, complexed BF_3) or solid ($AlCl_3$) [1]: their disadvantages are listed above;
- solid acids (e.g. zeolites, nafion silica composites or BEA-zeolites [9]), that have shown limits for this reaction due to relatively fast deactivation.

We demonstrate hereafter that methane sulfonic acid (MSA) is well suited to perform the rearrangement of phenyl acetate into *para*-hydroxyacetophenone with high conversion and selectivity.

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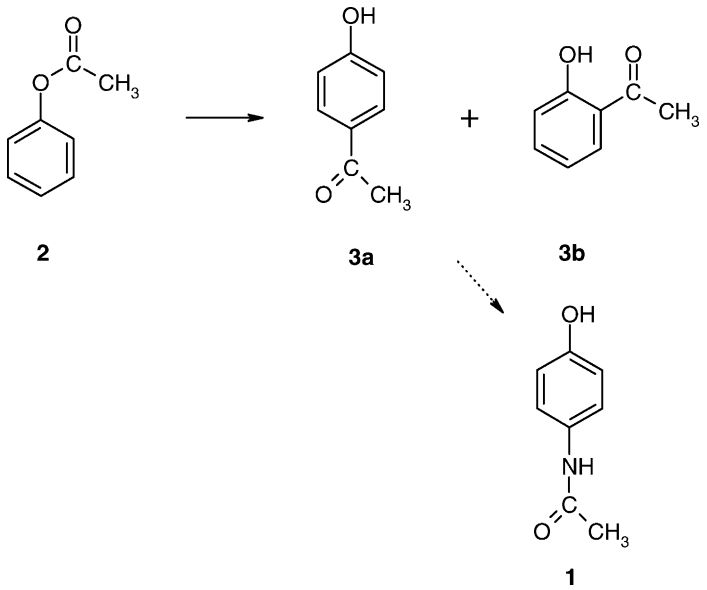

Scheme 1.

2. Background

MSA (CH_3SO_3H, CAS RN: 75-75-2) is a clear, colorless liquid available as a 70% solution in water and anhydrous forms.

The structure of MSA lends itself to many catalytic reactions, thanks to its high acid strength [15] ($pK_a = -1.9$) and low molecular weight (96.0 g/mol). MSA is less aggressive than sulfuric acid or HF. Moreover, MSA is an easy-to-handle liquid and often recyclable.

MSA has a reported LD_{50} (oral, rat) of 1158 mg g^{-1} [16]. It is considered as readily biodegradable (OECD 303A, OECD 301D closed bottle, OECD 301A Doc Die-away, BOD), ultimately forming sulfates and carbon dioxide. In fact, MSA is considered to be a natural product and is part of the natural sulfur cycle [17].

As a Brönsted acid, it is used either as homogeneous catalyst in widely used reactions (esterification, alkylation), as salification agent for amines (electro-coating processes, resin curing, active pharmaceutical ingredients), as catalyst and solvent for condensation or rearrangement reactions.

The use of MSA as catalyst in the Fries rearrangement is already known in the literature [8,10–14]. Usually, MSA is used as catalyst and solvent and the *ortho*-isomer is the major product. Only one example [8] describes the Fries rearrangement of phenyl acetate: MSA is used in catalytic amounts (maximum 28.6%), at temperatures between 160 and 196 °C, leading to conversions of around 20–30%. The undesired (in the case of paracetamol synthesis) *ortho*-hydroxyacetophenone **3b** isomer was the major product. The goal of this work was to show that MSA is able to catalyze the Fries rearrangement of **2** with good conversions and selectivities to the desired *para*-isomer **3a**.

3. Experimental

The exact conditions of each test are given in Table 1.

3.1. Reaction

In a 250 ml three-necked flask, equipped with a cooler and stirrer, phenyl acetate (99% pure, Aldrich) anhydrous MSA (99.5% pure, Atofina) and possibly phenol (99% pure, Prolabo) were mixed. The system was flushed with nitrogen and heated to the reaction temperature for the determined time. The medium turned red. The conversion was

Table 1
Fries rearrangement of phenyl acetate with MSA

Experiment	**2**	MSA	Solvent	T (°C)	Time (h)	Remaining **2** (wt.% by GC)	**3a** (wt.% by GC)	**3b** (wt.% by GC)	**3a**/**3b** ratio	0 **2** conversion (%)	**3a** + **3b** non-isolated yield (%)
1[a]	0.15 mol	0.02–0.08 mol	Phenol		1.5	62	9	4,5	2	40	
	1 equiv.	0.14 equiv. (4 times)		150	4.5	40	11	11	1	60	15
	20 wt.%	2 wt.% (4 times)			24	2	6	9.5	0.64	98	
2	0.15 mol	0.02 mol	Phenol		1.5	85	4	0	5.52	15	
	1 equiv.	0.14 equiv.		114	6.5	85	8	1	4.13	15	7
	20 wt.%	2 wt.%			20.5	1	6	1		99	
3	0.147 mol	0.208 mol	MSA	70	0.5	64	15	2	7.3	36	
	1 equiv.	1.42 equiv.		90	2.5	25	26	3.5	7.5	75	
	50 wt.%	50 wt.%			4	2	10.5	1	9.4	98	11.5
4	0.066 mol	0.22 mol	MSA		0.5	15	63	12	88.5	85	
	1 equiv.	3.3 equiv.		90	1.5	0	23		14	100	25
	30 wt.%	70 wt.%									
5	0.05 mol	0.4 mol	MSA								
	1 equiv.	8 equiv.		90	0.5	0	92	8	12.2	100	100
	15 wt.%	85 wt.%									
6	0.073 mol	1.98 mol	MSA		0.5	0	88	86	10	100	
	1 equiv.	27 equiv.		90	1	0	90		15	100	96
	5 wt.%	95 wt.%									
7	0.015 mol	0.117 mol	MSA/P_2O_5								
	1 equiv.	8 equiv.		90	0.5	0	52	1	44.4	100	53
	14 wt.%	86 wt.%									
8	0.015 mol	0.117 mol	MSA/P_2O_5								
	1 equiv.	8 equiv.		65	1.5	9	89	0			
	17 wt.%	86 wt.%			2.5	5	67	0		95	67

[a] For experiment 1 the MSA was added in four steps.

monitored by gas chromatography (HP5 column, 50 m × 0.32 mm × 0.52 μm, injector 300 °C, detector 280 °C, 6 min at 50 °C, 8 °C/min to 270 °C, 6 min at 270 °C). Retention times: phenol 17.4 min, phenyl acetate **2** 19.5 min, *ortho*-hydroxyacetophenone **3b** 22.4 min, *para*-hydroxyacetophenone **3a** 27.5 min. Sample prepared for GC by mixing 0.1 g of reaction medium to 0.5 g of dichloromethane and 1 g of water and the organic phase free from MSA was injected.

3.2. Isolation

At total phenyl acetate conversion 125 g dichoromethane was added, then the mixture was poured on crushed ice. After stirring for 1 h, the organic phase was separated and the aqueous phase extracted twice with 200 g of dichloromethane. The organic phases are combined and dried on magnesium sulfate. Dichloromethane was evaporated resulting in a crude product that was analyzed by GC and proton NMR (in $CDCl_3$, tetrachloroethane as internal standard).

4. Results and discussion

The experiments (1–8) are summarized in Table 1. Experiments 1 and 2 were performed in phenol as solvent with catalytic amounts of MSA (8% molar) at 115 or 150 °C. Despite total conversion of **2**, only 7% of **3a** and **3b** are obtained along with the degradation of the reaction medium.

Experiments 3–6 were performed at 90 °C without solvent using different amounts of MSA, from 1.4 to 27 molar equivalents. The optimum was found to be 8 equivalents (experiment 5). The weight ratio of MSA/**2** was 85–15. The same molar ratio was found in the literature with another substrate [10]. The reaction time was also important: 100% conversion of **2** was achieved after 1 h at 90 °C. Afterwards, the reaction has to be stopped to avoid degradation of the reaction medium (experiment 4).

The *para*/*ortho* ratio **3a**/**3b** was always in favor of the desired compound **3a** and decreased during the conversion of **2**. For example, in experiment 4 at 90 °C with an MSA/2 molar ratio of 3.3, the **3a**/**3b** ratio was 88 at 85% conversion of **2**. This ratio dropped to 14 at 100% conversion with only 25% of **3a** and **3b** due to degradation of the medium. Under optimized conditions (90 °C, molar ratio MSA/2 = 8 at 100% conversion), the *para*/*ortho* ratio was ca. 12 (experiment 5).

A preparative sample using the conditions of experiment 5 resulted in a crude product (94% yield) of 80% purity, with a **3a**/**3b** ratio of 10, the other product being phenol obtained upon hydrolysis of phenyl acetate **2**. It was found to be very important to use an anhydrous MSA, as traces of water immediately hydrolyze **2** to phenol and acetic acid. The purity as well as the *para*/*ortho* ratio were investigated with proton NMR as direct isolation of **3a** from MSA by distillation was not possible due to the close boiling points (147–148 °C under 3 mm Hg for **3a** and 167 °C under 10 mm Hg for MSA). Extraction experiments with other solvents which are not miscible with MSA like hexane, toluene or 2-chlorotoluene were unsuccessful.

To have a better reactivity, experiments with Eaton's reagent, a 7.7/100 wt./wt. Mixture of P_2O_5/MSA were performed, but were unsuccessful because of degradation of the reaction medium before completion of the reaction at 90 °C (experiment 7) or even at 65 °C (experiment 8). However, the **3a**/**3b** ratio of ca. 40 was very good (experiment 7).

5. Conclusion

MSA, a biodegradable liquid acid, was used in the Fries rearrangement of phenyl acetate **2** to *para*-hydroxyacetophenone **3a**, with very good conversions of around 100% and very good selectivities to the *para* product at an isomer ratio **3a**/**3b** around 10. To obtain such performances, a molar ratio of MSA/**2** of 8 were necessary, whereas in the HF Hoechst Celanese process a HF/**2** molar ratio of ca. 4 is used. After addition of water, the organic product was separated from the aqueous MSA phase by extraction with an organic solvent.

Compared to HF, a very toxic, volatile and environmentally unfriendly acid, MSA is a biodegradable and easy-to-handle liquid. It has very similar chemical performances (yield, conversion, selectivity) combined with a lower impact on the environment.

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