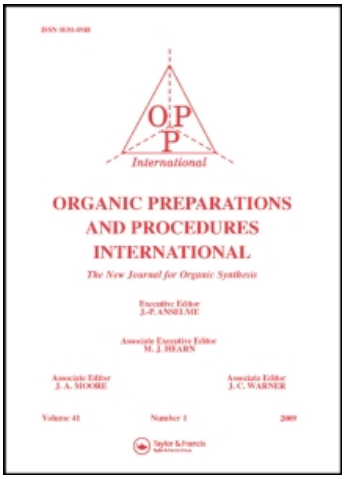

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EFFICIENT SOLVENT-FREE MICROWAVE-ASSISTED ESTERIFICATION OF FUSEL OIL USING *p*-TsOH AND $H_3PW_{12}O_{40}$ AS CATALYSTS

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Brazil is the world leader in the production of ethanol which exceeds 15 billions liters per year. Fusel oil, a by-product from the ethanol industry, is available in tens of millions liters per year. Fusel oil is basically composed of alcohols such as isopentanol (~45%) and isobutanol (~15%) with a small amount of esters (~2%).[1] The high content of various alcohols in fusel oil, in addition to the low cost ($0.15 per liter), provided the incentive to study an efficient, clean, and inexpensive technology for the use of fusel oil as a raw material to access a variety of esters. The synthesis of fatty esters derived from long-chain carboxylic acids ($C_{10} - C_{18}$) is a very important industrial process and applications as lubricants, surfactants, and cosmetic ingredients are widespread. Aromatic esters such as isopentyl benzoate are used in perfumes, while phthalates (*e.g.* isobutyl phthalate) are applied ubiquitously as plasticizers.[2]

Fischer-type esterifications are usually carried out under reflux with an excess of alcohol in the presence of strongly acidic catalysts. The use of desiccants or azeotropic distillation are commonly required to enhance yields. Several reports refer to the use of *p*-toluenesulfonic acid (*p*-TsOH),[3-5] sulfonated resins,[6] and zeolites[7] as useful catalysts for the esterifications. Heteropolyacids such as polyoxometalates, based on tungsten, vanadium and molybdenum, exhibit reversible and rapid redox behavior, (which is useful for oxidation) and high acidity which is appropriate for acid catalysis.[8-12] During recent years, non-conventional techniques are increasingly being applied in organic synthesis in order to improve yields and selectivities, and to have a more convenient work-up.[13-16] Special interest is focused on the application of microwave technology coupled with solvent-free conditions, allowing an expeditious entry into a new or an expanded field.[17-21]

We have now prepared lauric, stearic, benzoic, and phthalic esters by direct esterification of fusel oil with the corresponding carboxylic acids. These reactions were performed using a solvent-free microwave method and *p*-TsOH or $H_3PW_{12}O_{40}$ (HPW) as catalysts. Fusel oil was fractionated and the fraction with a boiling range of 124-130° proved to contain mainly isopentanol (93%) and isobutanol (6%). This fraction was used for the esterifications. Satisfactory conversions were obtained for isopentyl and isobutyl esters (Table 1), which were characterized by their mass spectra. Pure isopentanol served as a reference in order to optimize the experimental conditions. The output microwave power, exposure times, and acid/catalyst ratios were suitably adjusted and experiments were replicated to ensure reproducibility. No evidence of autocatalysis was observed, since esters were not detected in experiments carried out in the absence of *p*-TsOH or HPW (Table 1).

Lower yields for phthalates could be due to insufficient dissolution. In our experiments, when mixtures of two solid reactants were irradiated, one melted phase is observed as the temperature reached the melting point of one of the reactants or the eutectic point of the mixture. Sometimes, if the solids have low polarity (with low microwave's absorption), it necessary to add catalytic amount of some polar additives, such as dimethylformamide[15] as energy medium transfer in order to increase the temperature of the mixture.

Table 1. Microwave-assisted Catalytic Esterification of Acids

Acid	Alcohol	Catalyst [a]	Power (W); time (min); temperature (°C)	Conversion[b, c] (%) Isopentyl	Isobutyl
Lauric	Isopentanol	*p*-TsOH	480; 2:00; 125	97	
Lauric	Isopentanol	HPW	480; 2:00; 128	92	
Lauric	Fusel oil	HPW	480; 2:00; 128	88	80
Lauric	Isopentanol	None	480; 10:00; 124	<2	
Stearic	Isopentanol	*p*-TsOH	480; 1:20; 90	98	
Stearic	Isopentanol	HPW	480; 2:00; 118	80	
Stearic	Fusel oil	*p*-TsOH	480; 1:15; 119	90	89
Stearic	Isopentanol	None	480; 10:00; 112	<1	
Benzoic	Isopentanol	*p*-TsOH	480; 15:00; 112	94	
Benzoic	Isopentanol	HPW	480; 15:00; 114	67	
Benzoic	Fusel oil	*p*-TsOH	480; 15:00; 117	89	88
Benzoic	Isopentanol	None	480; 25:00; 112	<5	
Phthalic	Isopentanol	*p*-TsOH	80; 10:00; 98	84	
Phthalic	Isopentanol	HPW	80; 10:00; 100	15	
Phthalic	Fusel oil	*p*-TsOH	80; 10:00; 125	77	89
Phthalic	Fusel oil	None	160; 10:00; 118	<1	

a) Molar ratio acid/alcohol/catalyst = 1:2:0.1 (*p*-TsOH) or 1:2:0.01 ($H_3PW_{12}O_{40}$). b) For fusel oil, conversions are for isopentyl and isobutyl esters. c) Determined by hrgc and gc-ms on the basis of consumed carboxylic acid.

Significant differences in yields were observed on comparison of the effects of *p*-TsOH and HPW, respectively, on catalyzed esterifications of benzoic and phthalic acids. The HPW-catalyzed esterification of aromatic acids also gave unidentified by-products as detected by gc analysis. Preparations were scaled up to 50 mmoles carboxylic acids and 10 g fusel oil (~0.1 mole isopentanol) with satisfactory conversions to the corresponding esters (Table 2).

Table 2. Scale-up of Acid-catalyzed Esterification of Various Acids

Acid	Catalyst	Power (W); time (min); temperature (°C)	Conversion[a] (%) Isopentyl[b]	Isobutyl
Lauric	HPW	480; 2:00; 126	85 (82)	80
Stearic	*p*-TsOH	480; 1:20; 95	87 (85)	80
Benzoic	*p*-TsOH	480; 15:00; 119	85 (81)	75
Phthalic	*p*-TsOH	80; 10:00; 127	80 (77)	80

a) Determined by gc and gc-ms. b) Yields of isolated isopentyl esters in brackets.

The results obtained in up-scaled preparations recommend this protocol as an efficient, inexpensive, and clean method for the preparation of important esters using fusel oil as a low cost raw material. Salient features include the absence of solvent and the use of non-polluting and non-corrosive catalysts, thus representing an environmentally friendly approach. Furthermore, applications of $H_3PW_{12}O_{40}$ as a catalyst for preparations of esters under microwave irradiation are reported for the first time.

The synthesis of isopentyl stearate was performed using both microwave irradiation and conventional heating in solvent-free conditions at the same final temperatures and reaction times as measured in the microwave experiments. Results are given in Table 3.

Table 3. Synthesis of Isopentyl Stearate[a] using Microwave Irradiation (MW) and Conventional Heating (oil bath).

Heating	Time (min)	Temperature (°C)	Conversion[b] (%)
MW	**1:20**	**90**	**98 (96)**[c]
Oil bath	1:20	120	13
Oil bath	10:00	120	57

a) Stearic acid/isopentanol/*p*-TsOH 1:2:0.1; output power: 480 W. b) Determined by gs-ms.
c) Yield of isolated ester in brackets.

The dielectric environment during microwave-assisted preparation of esters could favor formation of polar intermediates, while rapid volatilization of water would shift the equilibrium favorably. Variations noted with respect to final temperatures (Tables 1 and 2) are related to the nature of the substrate and the catalyst. Polar molecules absorb the microwave irradiation more strongly and rapid increases of temperatures are observed. On the other hand, in addition to the satisfactory yields obtained, the short reaction times offer a major advantage of solvent-free microwave-induced esterifications. Studies are planned with the aim to use a microwave reactor equipped with infrared temperature detection, hence temperature profiles in esterifications of fusel oil, will be better controlled and we could improve the conversion to ester avoiding the loss of alcohols.

EXPERIMENTAL SECTION

Solvents were hplc grade from Merck, *p*-TsOH was purchased from Fluka, and $H_3PW_{12}O_{40}$ from Aldrich. Reactions were carried out in a Continental domestic microwave oven equipped with a turntable plate, which allows selection of the output power up to 800 watts. Conversions were determined by GC analyses performed using a HP 5890 gas chromatograph equipped with a flame ionization detector and a HP-5 column (25 m x 0.20 mm x 0.33 mm). The temperature of both the injector and the detector was fixed at 300°. GC-MS analyses were carried out using the HP 5890 gas chromatograph coupled to a HP 5970 Series Mass Selective Detector. A HP-1 column (50 m x 0.20 mm x 0.33 mm) was used. The temperature of both the injector and the interface was set at 300°. Fusel oil esters were separated and collected by semi-preparative HPLC using a Shimadzu C-R4A Chromatopac apparatus equipped with a UV-VIS spectrophotometric detector and a RP-18 column. Compounds were eluted with 40% aqueous methanol and the esters were detected by their absorbance at 254 nm. IR spectra of isopentyl esters were recorded on a Bomen FTIR spectrometer. The elementary analyses of isopentyl laurate were performed on an EA 1110 CE Instruments apparatus. Isobutyl esters from fusel oils were just characterized by their mass spectra.

Esterification Procedure. - Solvent–free microwave experiments were carried out by addition of 2 g (ca. 20 mmoles isopentanol) of a fusel oil distillate (bp. 124-130°) to a previously homogenized mixture of the appropriate carboxylic acid (10 mmole) and the catalyst (*p*-TsOH 10% mol/acid or HPW 1% mol/acid). The resulting mixture was poured into an open Pyrex-glass vessel and irradiated in an 800 W microwave oven using the experimental conditions indicated in Table 1. The temperature was measured after termination of the reaction. On cooling and filtration, the catalysts and the residual carboxylic acids were recovered. Isopentyl esters were isolated by distillation. The mains of esters were obtained as colorless liquids at 30°. Isopentyl benzoate was obtained as a pale yellow liquid.

Isopentyl Laurate, bp. 170° (2mm Hg). IR(KBr): 1738(CO) cm^{-1}. MS(m/z): 270 m^+; 227; 183; 83; 70.

Anal. Calcd for $C_{17}H_{34}O_2$: C, 75.55; H, 12.22. Found: C, 75.35; H, 11.95

Isobutyl Laurate, MS(m/z): 256 m^+; 213; 183; 83; 70. **Isopentyl Stearate**, mp. 24-25°, *lit.*[22] 25.5°. IR(KBr): 1738(CO) cm^{-1}. MS(m/z): 354 m^+; 284; 267; 241; 129; 70. **Isobutyl Stearate**, MS(m/z): 340 m^+; 284; 267; 241; 70. **Isopentyl Benzoate**, bp. 260°, *lit.*[22] 261-262°. IR(KBr): 1730(CO) cm^{-1}. MS(m/z): 192 m^+; 175; 163; 123; 105; 77. **Isobutyl Benzoate**, MS(m/z): 178 m^+; 163; 123; 105; 77. **Isopentyl Phthalate**, bp. 224° (40mm Hg), *lit.*[22] 225° (40 mm Hg). IR(KBr): 1728(CO) cm^{-1}. MS(m/z): 306 m^+; 237; 219; 149; 104. **Isobutyl Phthalate**, MS(m/z): 278 m^+; 223; 205; 149; 104.

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THE PREPARATION OF 1-ALLYLURACIL. *N*(1)-ALKYLATION OF *N*(3)-PROTECTED URACIL DERIVATIVES

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Acyclic and carbocyclic analogs of nucleosides have received a great deal of attention in recent years due to their potential use as antiviral and anticancer agents.[1] *N*-Allylated uracils are also known to possess significant biological activity.[2,3] Monoalkylation of uracil or thymine is most often not regioselective, *N*(1),*N*(3)-dialkylated products usually accompanying *N*(1)- or *N*(3)-monoalkyl derivatives.[4] Therefore the selective *N*(1)-alkylation of pyrimidine bases is of utmost importance. Since we required *N*(1)-allyluracil (**1**) for further synthetic elaboration, a high yield, inexpensive and selective method for its preparation was desired.

Allylation of uracil, thymine and cytosine with triallyl phosphite gave low yield of *N*(1)-allyl derivatives,[5] while the use of allyl bromide in basic solution led to a mixture of *N*(1)- and *N*(3)-monoallyl- and diallyl derivatives in low yield.[3,6] Pd(0)-catalyzed allylation of a thymine derivative with allyl acetate resulted in formation of *N*(1)-allyl and *N*(1),*N*(3)-diallyl derivative.[7] Regioselectivity of allylation was solvent and catalyst dependent.[8] Alkylation of 4-methylthio-5-fluoropyrimidin-2-one gave 65% yield of 1-allyl-5-fluorouracil.[9] 1-Allyluracil (**1**) was obtained by direct alkylation of uracil in 47% yield along with the 1,3-diallyl compound which could be removed by recrystallization.[10] With a bulky alkylating agent such as the adamantane derivative, regioselective *N*(1)-alkylation has been achieved under phase-transfer catalysis.[11] Selective *N*(3)-alkylation of *N*(1)-protected uracil has also been described.[12] When we attempted to alkylate uracil with allyl bromide-potassium carbonate in DMF solution[6] 1-allyluracil (**1**) could be isolated, albeit in low yield. The present communication describes an effective procedure for the selective *N*(1)-alkylation of uracil.