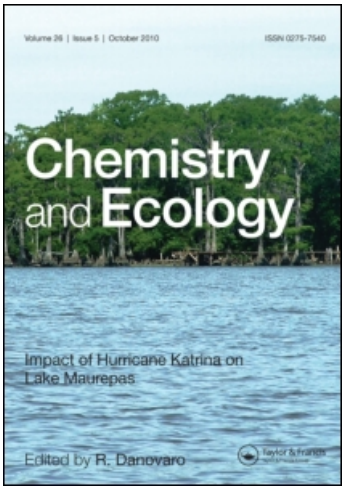

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CHEMICAL SYNTHESIS OF 6-PENTYL-2*H*-PYRAN-2-ONE: A NATURAL ANTIFUNGAL BIOSYNTHESIZED BY *TRICHODERMA* SPP.

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Trichoderma spp. biosynthesize 6-pentyl-2*H*-pyran-2-one (6-PP), a natural antifungal pyrone which could be used as biological control agent (BCA). Unfortunately, biotechnical processes are limited by inhibition of biomass at high concentration of 6-PP. We report herein a new easy synthesis of this natural pyrone, using readily available starting materials. This synthesis, compatible with a large production scale, permit to obtain overweight amounts of 6-PP that in biotechnological routes.

Keywords: 6-Pentyl-2*H*-pyran-2-one; Pyrone; *Trichoderma* spp.; Antifungal; Biotechnology; Synthesis

1 INTRODUCTION

The use of microorganisms as biological control agents (BCAs) seeks to restore the beneficial balance of natural ecosystems. *Trichoderma* spp. have proved to be useful BCAs, the best strains producing high quantities of 6-pentyl-2*H*-pyran-2-one (6-PP). Although production of 6-PP by *Trichoderma* spp. has been recognized as important factor of the antagonism mechanisms. This pyrone inhibits the growth of a range of phytopathogens, such as *Ceratocystis piceae*, *Armillaria*, *Botrytis cinerea*, *Rhizoctonia solani* (Claydon *et al.*, 1987; Hill *et al.*, 1997).

The production by biotechnology of 6-PP in various systems has been largely reviewed (Abou Zeid *et al.*, 2000; Bonnarme *et al.*, 1997; Cooney *et al.*, 1997; Merlier *et al.*, 1984; Prapulla *et al.*, 1992; Tekin *et al.*, 1995; Worasatit *et al.*, 1994).

The major problem of this production is inherent by the fact that inhibition of biomass growth occurs at low concentration of 6-PP (Serrano-Carreon *et al.*, 2002).

A lot of ameliorations of the biotechnological process have been reported (Alberto De Araujo *et al.*, 2002; Kalyani *et al.*, 2000; Rito-Palomares *et al.*, 2001; Sarhy-Bagnon *et al.*, 1997, 2000).

Previous syntheses make use of complexes strategies, toxic substances and/or drastic conditions: reactions of α-oxo ketene dithioacetals with organocuprate reagents (Dieter and

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Fishpaugh, 1988), Friedel-Crafts conditions followed by cyclization of the obtained keto-esters at 490 °C with copper, nickel, stainless steel catalysts (Pittet and Klaiber, 1975, Klaiber and Pillet, 1976).

Some recent and elegant syntheses have been depicted, but also utilize toxic reagents or are not compatible with a large scale production: palladium/copper-catalyzed reactions with 1-alkynes (Biagetti *et al.*, 2002), Stille palladium-catalyzed annulation of vinylstannanes by acyl chlorides (Thibonnet *et al.*, 2002), use of organozinc compounds or palladium-catalyzed reactions of organozincs with activated alkenyl halides (Bellina *et al.*, 2001), nickel-catalyzed coupling reactions of alkynes with halopropenoates (Kotora *et al.*, 1999).

We have been reported recently new syntheses of 6-PP from 2-methyl-heptan-2-one (Valla *et al.*, 2000) and methyl hexanoate (Giraud and Andriamialisoa, 2001).

2 RESULTS AND DISCUSSIONS

For economical purposes, we have investigated a modification of the latter patent (Giraud and Andriamialisoa, 2001), in order to produce a synthesis which could be realized with inexpensive and safe reagents.

The scheme of the synthesis is depicted in Figure 1.

Hence, lithium (or sodium) anions of dimethylsulfoxide (DMSO) react with methyl caproate to furnish the sulfoxide **2** in 80% yields. A Michael reaction of the anion of sulfoxide **2** (which could be generated with NaH, BuLi or *t*BuOK) with methylacrylate, lead to the ester **3** in 60% yield. The latter is saponified with potassium hydroxide to give the sulfinyl-acid **4** (80%) which underwent thermal elimination of the sulfoxide in boiling toluene/calcium carbonate to provide a crude mixture of acids **5a** and **5b** (100%). Cyclization in boiling acetic anhydride of the crude mixture led to the 6-PP **6** in a closely quantitative yield.

The substitution of the expensive methyl phenylsufoxide by dimethylsulfoxide and ethyl-3-bromopropionate by methyl acrylate (depicted in Giraud and Andriamialisoa, 2001) allow to produce 6-PP with a lower cost and therefore in a large scale. This synthesis,

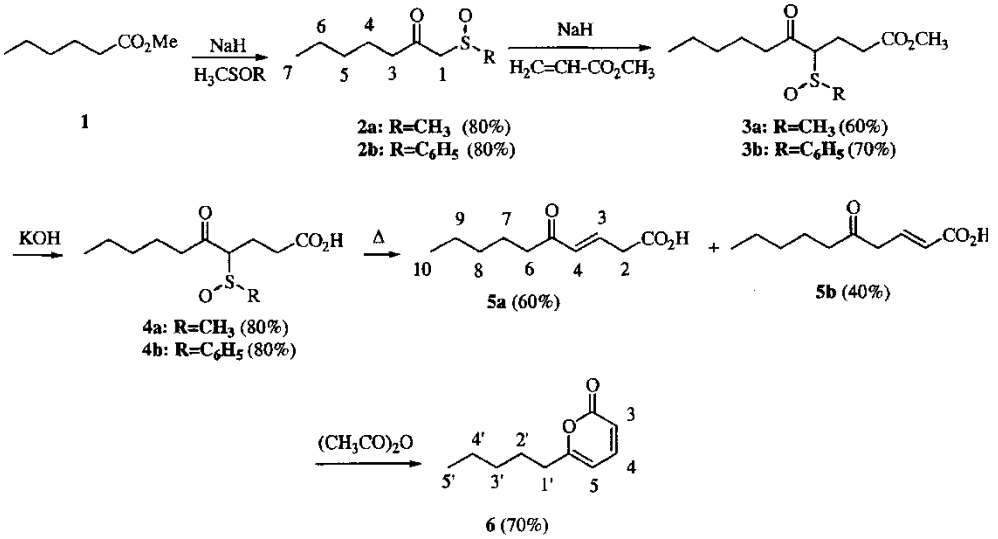

FIGURE 1

realized in four steps (overall yield 27%), allows the production of an ecological antifungal reagent which could be utilized in many ecological systems. In addition, all solvents (THF, ethyl acetate, methanol) used in this process could be easily recycled.

3 EXPERIMENTAL

1-Methyl-sulfinyl-2-heptanone **2a**. To a stirred suspension of NaH (50% in mineral oil, 50 g, 1 mol) in THF (300 mL) at 70 °C is added dropwise a solution of DMSO (100 mL, 1.26 mol) in THF (100 mL). The mixture is stirred for 3 hrs, cooled at 0 °C and a solution of methyl caproate (65 g, 0.5 mmol) is added dropwise. After 4 hrs at rt, the crude solution is hydrolysed (HCl 50%), extracted with ethyl acetate and chromatographied (SiO_2; ethyl acetate). The 1-methyl-sulfinyl-2-heptanone is obtained in 80% yield as a colourless oil. IR (film) ν_{CO}: 1700. ^{1}H NMR: 3.79 (*d*, 1H, $J = 16.0$, H_1); 3.69 (*d*, 1H, $J = 16.0$, H'_1); 2.67 (*s*, 3H, $SOCH_3$); 2.58 (*m*, 2H, H_3); 1.58, 1.27 (2*m*, 4H, H_5, H_6); 0.86 (*t*, 3H, $J = 7.0$, H_7). ^{13}C NMR: 202.5 (C_2); 68.9 (C_1); 45.2 (C_3); 38.9 ($SOCH_3$); 30.9, 22.7, 22.2 (C_4, C_5, C_6); 13.7 (C_7).

Methyl-4-methyl-sulfinyl-5-oxo-decanoate **3a**. To a stirred suspension of NaH (50% in oil, 5 g; 100 mmol) in THF (100 mL) at 0 °C is added dropwise a solution of 1-methyl sulfinyl-2-heptanone (23 g, 100 mmol) and methyl acryl ate (12.75 g, 150 mmol). in THF (100 mL). The solution is stirred for 4 hrs and then hydrolyzed by a solution of 20% HCl. After extraction with ethyl acetate and purification by column chromatography (SiO_2 ethyl acetate), the ethyl-4-phenyl-sulfinyl-5-oxo-decanoate is obtained as a pale-yellow oil mixture of diastereomers, in 60% yield. IR (film) ν_{CO}: 1730. ^{1}H NMR: 4.00 and 3.80 (2*m*, 2H, H_4); 3.80, 3.75 (2*s*, 3H, OCH_3); 2.80, 2.62 (2*m*, 4H, H_2 and H_3); 2.55, 2.50 (2*s*, 3H, $SOCH_3$); 2.15, 2.00, 1.75, 1.40 (*m*, 6H, H_2, H_3, H_5); 1.80, 1.40 (*m*, 3H, H_7, H_8, H_9); 0.90 (*t*, 3H, $J = 7.0$, H_{10}).^{13}C NMR: 204.6 (C_5); 172.4 (C_1); 70.5, 68.4 (C_4); 51.8 (OCH_3); 46.7, 44.9 (C_6); 35.4, 34.4 ($SOCH_3$); 32.1, 31.0, 22.6, 22.5, 22.3, 20.3, 18.8, 15.1 (C_7, C_8, C_9); 15.1, 13.8 (C_{10}).

Methyl-4-methyl-sulfinyl-5-oxo-decanoic acid **4a**. To a stirred suspension of **3a** (26.6 g, 100 mmol) in water (100 mL) is added a 1 M solution of methanolic KOH (120 mL, 120 mmol). After 14 hrs at rt, the mixture is washed with ethyl acetate and the aqueous layer is acidified with 10% HCl and extracted with ethyl acetate. The crude product is obtained as a mixture of diastereomers, in 80% yield. IR (film) ν_{CO}: 1710. ^{1}H NMR (DMSO *d-6*): 4.00 and 3.90 (2*m*, 2H, H_6); 2.80 (*s*, 1H, OH); 2.20 and 2.18 (2*s*, 3H, $SOCH_3$); 2.10, 2.00, 1.90, 1.80, 1.70 (5*m*, 8H, H_6, H_7, H_8, H_9); 0.80 (*t*, 3H, $J = 7.0$, H_{10}).^{13}C NMR (DMSO *d-6*): 205.7 (C_5); 173.8, 173.7 (C_1); 70.2, 68.6 (C_4); 44.7, 39.9 (C_2); 35.1, 31.3 ($SOCH_3$); 31.0, 30.9, 22.5, 22.4, 22.3, 20.0, 19.9 (C_3, C_6, C_7, C_9); 14.1 (C_{10}).

5-Oxo-2-decenoic and 5-oxo-3-decenoic acids **5a** and **5b** (Valla *et al.*, 2000). A solution of **4a** (21.6 g, 100 mmol) in toluene and $CaCO_3$ (10 g, 100 mmol) is heating at 90 °C for 6 hrs. The crude acids are extracted with a saturated solution of $NaHCO_3$. After acidification (HCl 1 M) and extraction with ethyl acetate, the solvent is removed under reduced pressure and the crude mixture is used without any purification (100%) in the next step. From this mixture, **5a** and **5b** (60/40) were separated by column chromatography (SiO_2, CH_2Cl_2/CH_3OH: 98/2).

5-Oxo-3-decenoic acid **5a**: IR (film) ν_{CO}: 1710. ^{1}H NMR ($CDCl_3$): 7.15 (*dt*, 1H, $J = 16.0$, $J = 7.0$, H_3); 5.87 (*d*, 1H, $J = 16.0$, H_2); 3.35 (*d*, 2H, $J = 7.0$, H_4); 2.60 (*t*, 2H, $J = 7.0$, H_6); 1.60; 1.33 (2*m*, 6H, H_7, H_8, H_9); 0.85 (*t*, 3H, $J = 7.0$,H_{10}).

5-Oxo-2-decenoic acid **5b**. IR (film) ν_{CO}: 1710. ^{1}H NMR ($CDCl_3$): 6.87 (*dt*, 1H, $J = 16.0$, $J = 7.0$, H_2); 6.18 (*d*, 1H, $J = 16.0$, H_3); 3.28 (*d*, 2H, $J = 7.0$, H_4); 2.60(*t,* 2H, $J = 6.0$, H_6); 1.60; 1.33 (2*m*, 6H, H_7, H_8, H_9); 0.85 (*t*, 3H, $J = 7.0$, H_{10}).

6-PP **6**. A mixture of **5a** and **5b** (1.8 g; 10 mmol) in $(CH_3CO)_2O$ (10 mL) is heated at reflux for 2 hrs. After cooling and solvent evaporated 6-PP is obtained in 70% yield, as a colourless oil. IR (film) ν_{CO}: 1730. ^{1}H NMR ($CDCl_3$): 7.26 (*dd*, 1H, $J = 9.5$, $J = 6.5$, H_4); 6.15 (*dd*, 1H, $J = 9.5$, $J = 1.0$, H_3); 5.98 (*dd*, 1H, $J = 6.5$, $J = 1.0$, H_5); 2.48 (*t*, 2H, $J = 7.5$, $J = 1.0$, $H_{1'}$); 1.66 (*m*, 2H, $H_{2'}$); 1.32 (*m*, 4H, $H_{3'}$, $H_{4'}$); 0.90 (*t*, 3H, $J = 70$, $H_{5'}$). ^{13}C NMR: 166.7 (C_2); 143.6, 112.9, 102.5 (C_3, C_4, C_5); 33.6, 31.0, 26.4, 22.2 ($C_{1'}$, $C_{2'}$, $C_{3'}$, $C_{4'}$); 13.8 ($C_{5'}$).

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