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ENZYMATIC SYNTHESIS OF PROPARGYLAMIDES

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Summary: A lipase (Candida cylindracea) catalyzed the reaction between ethyl propiolate and aromatic amines to afford propargylamides.

The potential of enzymes as practical catalysts for organic synthesis in nonaquous media is becoming increasingly recognized.[1] In particular, lipases have been widely used for the resolution and preparation of chiral alcohols, ethers and carboxylic acids through the corresponding asymmetric esterification or transesterification reactions.[2] However, the utility of these enzymes in the preparation and resolution of different nitrogen organic compounds has hardly been investigated.

We have shown that porcine pancreatic lipase (PPL) and yeast Candida cylindracea (CCL) catalize the enantioselective acylation of aminoalcohols,[3] and the formation of chiral amides.[4] Recently, Klibanov and col. have described an enzymatic resolution of racemic amines using subtilisin in anhydrous 3-methyl-3-pentanol.[5] In order to broaden the utility of enzymes in the synthesis of amides, we have investigated the catalytic potential of lipases towards ethyl propiolate and aromatic amines in organic solvents. In the present communication, we report that yeast lipase (CCL) can be used for the preparation of propargylamides.

Ethyl propiolate reacts with amines to give the corresponding product of addition of Michael(3).[6] The reaction rates are significantly higher in the case of aliphatic amines than when aromatic amines are used. Accordingly, we thought it interesting that in the case of aromatic amines, a lipase could lead the reaction towards the formation of the amide **4**.

The general reaction catalized by yeast lipase is as follows: A mixture of (1) (5 mmol) and (2) (4 mmol) was dissolved in tetrachloromethane (25 mL), and then 4 g of CCL was added. The suspension was vigorously shaken at room temperature and periodically the liquid phase

was analyzed by IR. After 3-4 days the reaction was stopped, the enzyme removed by filtration and the solvent evaporated, the propargylamides (4) were obtained with high yields (see Table).[7]

In contrast to CCL, porcine pancreatic lipase showed a very low catalitic activity and with papain only the adduct of Michael (3) was isolated.

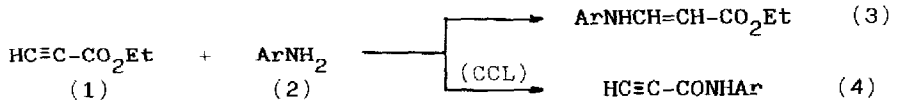

Table: Propargylamides (**4**) from (**1**) and aromatic amines (**2**) with yeast lipase in tetrachloromethane.

Entry	Ar	Reaction time, h (T,°C)	Yield,%	mp.°C
(**4a**)	C_6H_5	96 (25)	80	81-83
(**4b**)	4-CH_3O-C_6H_4	72 (25)	85	96-98
(**4c**)	4-CH_3-C_6H_4	96 (25)	82	126-128
(**4d**)	4-Cl-C_6H_4	96 (60)	60	172-174

In conclusion, the strategy described here provides an easy method of obtaining propargylamides (4), which, to the best of our knowledge, have not been described previously. Some amides derived from propiolic acid are found as bactericides.[8]

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7.- Compound (**4a**): IR (KBr) 2110 and 1635 cm^{-1}, δ_H (300 MHz, $DCCl_3$) 1.62 (s, 1H, exch. with D_2O), 2.94 (s, 1H) and 7.70-7.10 (m, 5H) ppm; δ_C (75 MHz, $DCCl_3$) 74.16 (d), 77.46 (s), 120.03 (d), 125.09 (d), 128.99 (d), 136.88 (s) and 149.81 (s) ppm.; mass spectrum (70 ev) m/e: 145 (M^+).

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