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Chemoenzymatic Aminolysis and Ammonolysis of β-Ketoesters

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Abstract: *Candida antarctica* lipase efficiently catalyzes the preparation of β-ketoamides from β-ketoesters with primary aliphatic amines and ammonia.

The preparation of β-ketoamides is an interesting task because these compounds are highly versatile intermediates in organic synthesis. One of the most efficient routes for the preparation of amides is the direct aminolysis of esters. However, the aminolysis of β-ketoesters requires high temperature, long reaction times, and only low yields of β-ketoamides are obtained due to the competitive enaminoester formation.[1] Higher yields are obtained when DMAP is used as catalyst,[2] but high temperature is required too. An interesting alternative is the room temperature aminolysis of the β-ketothioester derivatives,[3] but these substrates are not so readily available.

Here we report the direct conversion of β-ketoesters in β-ketoamides by lipase catalysed aminolysis and ammonolysis.

Candida antarctica lipase has proved to be an efficient catalyst in the enantioselective aminolysis of (±)-3-hydroxyesters[4] and acrylic esters.[5] We have used this catalyst in the aminolysis of some β-ketoesters with primary aliphatic amines such as butyl, benzyl, allyl and dodecylamine.[6] The reactions were carried out at 30°C using dioxane as solvent and with a molar 1:1 ratio ester-amine. In these conditions, β-ketoamides[7] were obtained with very high yields (see Table). If an excess of amine is used in the enzymatic reaction (1:1.5 molar ratio), a mixture of enaminoamide (**5**) and β-ketoamide (**3**) is obtained. However, the enzyme only catalyzes the aminolysis of the β-ketoester, since unchanged compound **4** (prepared from **1** and amines **2** in absence of the lipase) is recovered when the enaminoester (**4**) is allowed to react with the amine in presence of the enzyme.

In addition, CAL has also shown a very high catalytic efficiency in the ammonolysis of β-ketoesters (Table). These reactions were carried out at 30°C using a 2% solution of ammonia in dioxane. The mildness of these reaction conditions and the high yields of the *N*-unsubstituted β-ketoamides obtained are noteworthy.

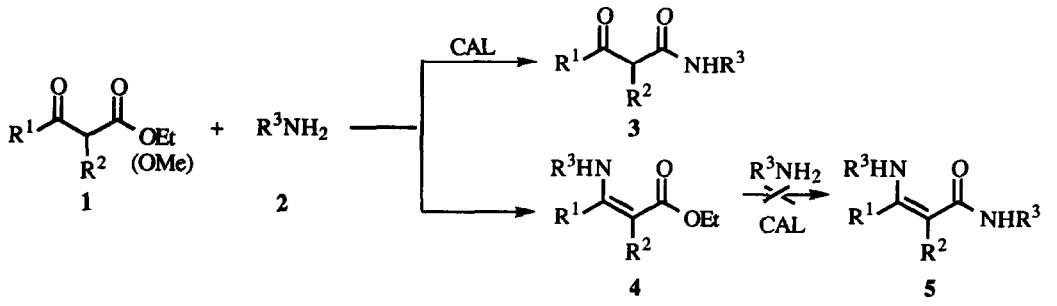

Table. Aminolysis and ammonolysis of **1** catalyzed by CA lipase

Entry	R^1	R^2	R^3	mp,°C	t, h	Yield, %	Entry	R^1	R^2	R^3	mp,°C	t, h	Yield, %
3a	Me	H	Bu	38-9	16	90	**3e**	$-(CH_2)_3-$		$PhCH_2$	85-6	48	71
3b	Me	H	$PhCH_2$	101-2	18	89	**3f**	Me	H	H	oil	24	59
3c	Me	H	Allyl	oil	16	91	**3g**	$-(CH_2)_3-$		H	97-8	15	90
3d	$-(CH_2)_3-$		Bu	oil	48	72	**3h**	Ph	H	H	94-5	68	92

In conclusion, we have developed a very simple and practical method to obtain β-ketoamides by the direct aminolysis and ammonolysis of β-ketoesters. The study of the enantioselectivity of this enzymatic process using racemic amines is currently under investigation.

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REFERENCES AND NOTES

1. Williams, J. W.; Krynitsky, J. A. *Org. Synth. Coll. Vol. III*, **1955**, 10.
2. Cossy, J.; Thellend, A. *Synthesis*, **1989**, 753.
3. Ley, S. V.; Woodward, P. R. *Tetrahedron Lett.*, **1987**, *28*, 3019.
4. García, M. J.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry*, **1992**, *3*, 1519.
5. Puertas, S.; Brieva, R.; Rebolledo, F.; Gotor, V. *Tetrahedron*, **1993**, *49*, 4007.
6. Typical run: To a solution of ester **1** (2.5 mmol) and amine **2** (2.5 mmol) in dioxane (20 ml) was added *Candida antarctica* lipase (300 mg). The reaction was stirred at 250 rpm at 30°C. If necessary, compounds **3** were purified by flash column chromatography using hexane-ethyl acetate 2:1 as eluent.
7. Compound **3c**: IR (neat) 1721 and 1645 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 2.30 (s, 3H, CH_3), 3.46 (s, 2H, CH_2), 3.92 (m, 2H, CH_2), 5.12-5.30 (m, 2H, CH_2), 5.76-5.95 (m, 1H, CH), 7.2 (bs, 1H, NH). ^{13}C-NMR ($CDCl_3$) δ: 30.13 (CH_3), 41.33 (CH_2), 49.86 (CH_2), 115.57 (CH_2), 133.34 (CH), 165.74 (C=O), 203.60 (C=O). MS (70ev) *m/z*: 141 (M^+, 5), 56 (100).

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