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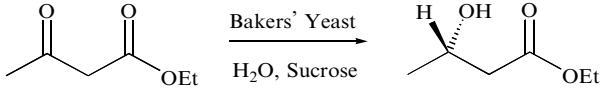
10 Asymmetric Reduction of Ketones Using Bakers' Yeast

CONTENTS

10.1 BAKERS' YEAST REDUCTION OF ETHYL ACETOACETATE

Among the strategies developed for the preparation of optically active ester derivatives, the bakers' yeast reduction of the corresponding β-ketoesters is one of the most useful methods. Because of its low cost, ready availability and its utility, bakers' yeast can be considered as a relatively simple reagent which is very easy to handle[1–3].



Materials and equipment

- Ethyl acetoacetate, 9.8 mL, 10.0 g, 77 mmol
- Bakers' yeast (*Saccharomyces cerevisiae*), Sigma Type II, 20 g
- Sucrose, commercially available table sugar, 150 g
- Celite® or hyflo super cell, 20 g
- Tap water, 650 mL
- Sodium chloride
- Ethyl acetate, dichloromethane
- *p*-Anisaldehyde

- Magnesium sulfate

- 2 L three-necked round-bottomed flask
- Bubbler
- Thermostatically controlled oil bath and thermometer
- Orbital shaker at 30 °C and 220 r.p.m. (optional)
- Wide sinter funnel
- Magnetic stirrer plate
- Rotary evaporator
- Kugelrohr apparatus

Procedure

1. A 2 L three-necked round-bottomed flask equipped with a bubbler and a thermometer was charged with tap water (400 mL), sucrose (75 g) and dried yeast (10 g), added in this order. The mixture was stirred very gently (150 r.p.m.).

   After 1 hour, carbon dioxide should be evolved at approximately 1–2 bubbles/second. Alternatively the whole reaction may be carried out in a 2 L conical-flask placed in an orbital shaker at 30 °C and 220 r.p.m.
2. Ethyl acetoacetate (5 g) was then added dropwise to the fermenting solution and the mixture stirred at ambient temperature for 24 hours.
3. A warm solution (40 °C) of sucrose (50 g) in tap water (250 mL) was then added and the mixture stirred for 1 hour before a further aliquot of ethyl acetoacetate (5 g) was added. The mixture was then stirred for a further 18 hours.
4. The reaction was followed by TLC (eluent: dichloromethane). The starting material was UV active, stained yellow with *p*-anisaldehyde, R_f 0.75.

   At this stage a very slight trace of ethyl acetoacetate could be seen by TLC and to assist further reduction more sucrose (25 g) and yeast (10 g) were added. The reaction was then stirred at 30 °C for 18 hours.
5. When no more starting material was apparent by TLC, the reaction was considered to be complete.

   It is essential that all the starting material is consumed before terminating the reaction.
6. Celite® or hyflo super cell (20 g) was added to the suspension which was then filtered through a pad of hyflo in a wide-sinter funnel; the pad was washed with water (100 mL). The filtrate was saturated with sodium chloride and then extracted with ethyl acetate (5 × 500 mL). The combined extracts were dried over magnesium sulfate, filtered and the solvent was removed under reduced pressure to afford a pale viscous oil.
7. The crude product was then distilled using Kugelrohr apparatus (56 °C, 12 mmHg) to afford the desired alcohol as a clear colourless oil (5.80 g, 57 %).

   $[\alpha]^{25}_{D} + 35.4^{\circ}$ (c 1.35, $CHCl_3$), [Lit. $[\alpha]^{25}_{D} + 37.2^{\circ}$ (c. 1.3, $CHCl_3$)] which corresponds to 80–85 % ee.

NMR ^{1}H (200 MHz, $CDCl_3$): δ 4.18 (m, 1H, C*H*); 4.17 (q, *J* 7.15 Hz, 2H, CH_2CH_3); 3.17 (brs, 1H, exchangeable with D_2O, O*H*); 2.45 (d, *J* 7 Hz, 2H, CH_2); 1.29 (t, *J* 7.15 Hz, 3H, CH_2CH_3); 1.23 (d, *J* 5.5 Hz, 2H, $CHCH_3$).

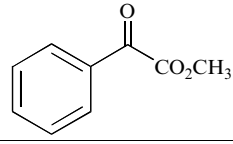
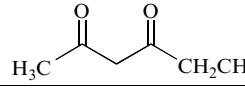
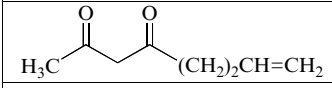
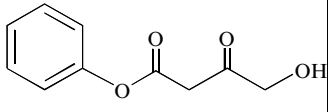
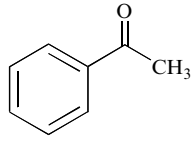
IR (Thin film, cm^{-1}): 3440, 2980, 1730, 1300.

Conclusion

In the original paper, the authors performed the reaction using commercially available bakers' yeast from a supermarket or bakery. Initially a trial run using similar quantities of Sigma dried yeast resulted in an extremely vigorous initial fermentation, so the quantity of dry yeast was reduced by factor of 5. The contributors assessed the enantiomeric excess of the alcohol by formation of the (+)-MTPA ester and examination of the ^{19}F NMR spectrum. However, the value obtained for the optical rotation was consistent with that reported in the literature.

Bakers' yeast is an inexpensive and readily available reducing agent that can be considered as a relatively simple reagent which is very easy to handle. Different substrates which can be reduced by bakers' yeast are reported in Table 10.1[1]; some other methods are described in a previous publication[4].

Table 10.1 Reduction of carbonyl compounds mediated by bakers' yeast (results according to the literature).

	Yield %	ee %
	59	100
	48–100 57*	>97 Ca 85*
	100	>99
	99	>99
	45	89

* Reaction validated

10.2 ENANTIOSELECTIVE SYNTHESIS OF (*Z*)-N-CARBOBENZYLOXY-3-HYDROXYPROLINE ETHYL ESTER

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10.2.1 IMMOBILIZATION OF BAKERS' YEAST

Materials and equipment

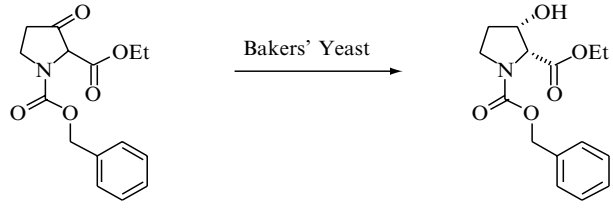
- Supermarket variety bakers' yeast, 20 g[5]
- Sodium alginate, 5 g
- Water, 200 mL
- 10 % (w/v) Calcium chloride, 670 mL

- 2 L Erlenmeyer flask
- Magnetic stirrer
- 1 L Dropping funnel

Procedure

1. Two separate solutions of Red Star active dry yeast (or other supermarket variety, 20 g) and sodium alginate (5 g) each in water (200 mL) were prepared by very slow addition of the respective reagent to the rapidly stirred solvent.
2. When each solution became an homogeneous viscous fluid, they were combined and added dropwise via an addition funnel to calcium chloride (670 mL of 10 % (w/v)). The droplets formed gelatinous beads upon impact with the salt solution. The size and shape of the beads may be adjusted by the rate of addition.
3. The beads were washed five times with water (portions of 500 mL), and used immediately in the reduction of ketone.

10.2.2 BAKERS' YEAST REDUCTION OF (*Z*)-N-CARBOBENZYLOXY-3-KETOPROLINE ETHYL ESTER



Materials and equipment

- Immobilized Bakers' Yeast, 200 g
- Sucrose, 40 g
- *N*-CBZ-3-Ketoproline ethyl ester, 5.64 g
- Ethanol, 10 mL
- Celite

- 2 L Erlenmeyer flask
- Magnetic stirrer
- Dropping funnel
- Buchner funnel

Procedure

1. The beads from the previous procedure (~200 g) were placed into a 2 L Erlenmeyer flask containing a large magnetic bar. Distilled water was added to give ~950 mL total volume. Sucrose (40 g) was added and the mixture was allowed to stir vigorously for 30 minutes after which time a solution of the keto ester (5.64 g, 20 mmol) in ethanol (10 mL), was added over a period of ~3 hours. The reaction was monitored by TLC and stopped when most of the starting material had been consumed (no longer than 24 hours).
2. The aqueous liquid was decanted onto a bed of Celite in an 11 cm Büchner funnel. The remaining yeast beads were washed and decanted three times using ethyl acetate (200 mL portions). The beads were then pressed free of their liquid content by compression against the filter. The resulting yeast cake was rinsed with ethyl acetate (~100 mL) and the layers of the filtrate were then separated. The aqueous layer was saturated with sodium chloride, filtered through Celite to remove gelatinous emulsions, and then extracted with ethyl acetate (200 mL). The combined organics were dried over magnesium sulfate, filtered, and evaporated to give 5.53 g of the crude product.
3. The crude product may be purified by chromatography over silica gel (eluted with 1:1 ethyl acetate–hexane). Average purified yield ~85 %. R_f 0.35 (50:50 hexane:ethyl acetate).

   The optical purity and stereochemistry was established by conversion to the known *N*-BOC protected proline and by comparison of spectral data and rotation values[6]. Additionally, the optical purity was established by HPLC analysis of the 3,5-dinitrobenzoates on a Pirkle column and by Mosher ester analysis.

   ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.24–1.30 (m, 3H), 2.02–2.12 (m, 2H), 2.65 (s, 1H, broad), 3.53–3.58 (m, 1H), 3.69–3.73 (m, 1H), 4.08–4.15 (m, 1H), 4.22–4.26 (m, 1H), 4.41–4.46 (m, 1H), 4.59–4.62 (m, 1H), 5.04–5.19 (m, 2H), 7.29–7.36 (m, 5H).

   ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0 and 14.1, 32.0 and 32.8, 44.2 and 44.4, 61.2 and 61.3, 63.5 and 63.8, 67.1, 71.4 and 72.2, 127.7 and 127.8, 127.9

and 128.0, 128.3 and 128.4, and 136.3 and 136.5, 154.4 and 154.8, 169.8 and 170.0 (resonances are doubled due to hindered rotation).

Rotation was recorded on a JASCO-DIP-370 instrument: $[\alpha]_{D^{26}} + 21.87$ (*c* 1.996, CH_2Cl_2).

Conclusions

The reduction of β-keto esters by bakers' yeast is a convenient method for establishing multiple chiral centres in a single step. The procedure is very simple and can be carried out on a large scale. Isolation of the product is often problematic if one uses the yeast directly. The procedure using immobilized yeast allows for easy work up and higher chemical yield[7]. The present work is a modification of the procedure for the reduction of *N*-BOC-3-ketoproline ethyl ester originally reported by Knight *et al.*[8] The product hydroxyproline has served as a starting material in the synthesis of the indolizidine alkaloid slaframine[9].

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