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THE PREPARATION OF ENANTIOMERS OF PACLOBUTRAZOL : A CRYSTAL CHEMISTRY APPROACH

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Abstract

A practical method for preparing the desired enantiomer of an agrochemical is described. The unwanted enantiomer is recycled simultaneously. Development of the method necessitated an understanding of the organic, solution and crystal chemistry. The general applicability of the method depends in particular on the crystal chemistry.

I. Introduction

Paclobutrazol, (2RS, 3RS)-1-(4-chlorophenyl)-4, 4-dimethyl-2-(IH-1,2,4 triazol-1-yl) pentan-3-ol(Fig 1) is a racemate; the (2S,3S) enantiomer is a plant growth regulator[1]. Separation of the enantiomers is possible via diastereoisomeric salt formation[2],[3] but expensive. A further disadvantage is that the unwanted enantiomer cannot be readily recycled. Paclobutrazol is manufactured from the corresponding ketone (Fig 1). Starting from racemic (RS) ketone, sodium borohydride reduction gives only the (2RS, 3RS diastereoisomer.[3] Therefore separating the enantiomers of the ketone could give (2S,3S)-paclobutrazol, provided:

i) there is a viable separation method for the ketone enantiomers.
ii) the unwanted ketone enantiomer can be recycled easily.
iii) the resolved (S)-ketone can be reduced stereospecifically to give (2S,3S)-paclobutrazol.

These three criteria are concerned with the crystal, solution and organic chemistry respectively. The purpose of this paper is to show that these three criteria can be satisfied, giving a practical process for preparing enantiomerically pure paclobutrazol.

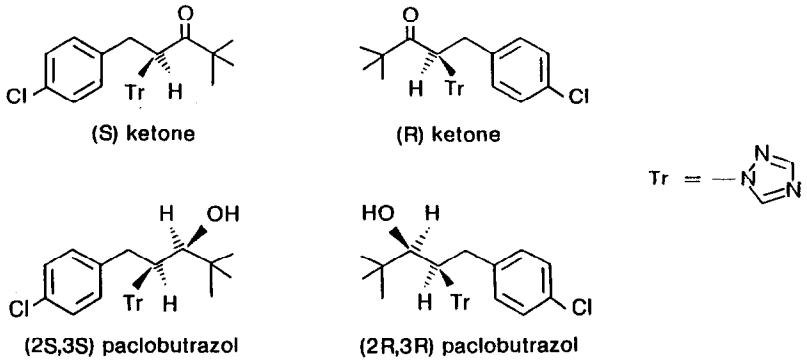

Fig 1. Enantiomers of paclobutrazol and the ketone.

2. Organic Chemistry: Stereospecific Reduction

It has been shown previously[3] that reduction of the (RS)-ketone with sodium borohydride gives the (2R,3R) and the (2S,3S)-enantiomers of the paclobutrazol. the same experimental method was used, with pure (R)-ketone as the starting material, to discover whether pure (2R,3R) paclobutrazol, or racemic paclobutrazol was produced.

The (R)-ketone starting material was analysed by HPLC (see appendix for details of the method) and found to be 100% enantiomerically pure. A 22% w/w slurry in methanol was prepared at 5°C, and 1% w/w solid sodium borohydride was added slowly, ensuring that the temperature stayed constant. The mixture was stirred for two hours at 5°C, then excess water (2.5x, w/w) was added and the temperature raised to ambient. The mixture was acidified to pH 1 with dilute hydrochloric acid, stirred for 20 minutes, rendered alkali with aqueous sodium hydroxide, and stirred for a further 20 minutes. The product was collected by vacuum filtration and water washed to give a white crystalline solid. The procedure was repeated using 100% enantiomerically pure (S)-ketone as starting material. Yields and analytical data are given in Table I. It was noted that the (2S, 3S) product was not 100% enantiomerically pure, possibly due to some ketone racemisation during hydrogenation.

Table I.

Starting Material	(R)-Ketone	(S)-Ketone
Yield of alcohol(%)	100	85
Purity(%,HPLC)	93.5	99.2
Optical Purity(%,HPLC)	100	95
Specific Rotation(589nm, methanol)	+132° (c=0.14%,25°C)	-127° (c=1%,19.5°)
Melting Point	148°C	151°C

Thus, starting from (S)-ketone, (2S,3S)-paclobutrazol can be prepared with only slight loss of enantiomeric purity.

3. Crystal Chemistry: Separation Method

When a racemate crystallises from solution, individual crystals may be enantiomerically pure (a "racemic mixture" or "conglomerate"), racemic (a "racemic compound"), or a solid solution of the two enantiomers[4]. Only in the first case will a seeded separation process be possible. Thus the crystal chemistry selects the appropriate separation method.

A single crystals grown by solvent evaporation from racemic ketone solution in methanol was selected for single-crystal X-ray structure determination. The space group observed was $P2_12_12_1$, with four molecules in the unit cell. Full structural details will be reported elsewhere. The crystal structure shows unambiguously that only one enantiomer is present in the structure. Thus it should be possible to prepare single crystals which are enantiomerically pure.

Several large single crystals were grown from recrystallised (RS)-ketone which was saturated in methanol at 35°C and then cooled slowly. Seeds were rotated slowly in the solution by means of a branched stirring rod attached to an RS Components 60rpm motor. Each of these crystals was ground up separately and analysed by chiral HPLC. One sample, which was found to contain 84% (S)-ketone, was used to seed a second crystal growth process. The resulting solid was then recrystallised from 3:1 w/w water/methanol to give 100% enantiomerically pure (S)-ketone. This confirms that individual crystals are not racemic, but contain an excess of one enantiomer. Hence seeding of a racemic solution with enantiomerically pure seeds prepared as above should give enantiomeric separation. Saturated solutions of racemic ketone in 3:1 wt/wt methanol water were prepared at 21±0.1°C. The solution was heated to 30°C for 30 minutes to ensure complete dissolution of any nuclei, then cooled rapidly to 20±0.1°C. 10mg (approx) of enantiomerically pure seed was added, and the solution was stirred for 4 hours. The resulting crystals were analysed by chiral HPLC as described above. Analysis showed that the product crystals were 100% enantiomerically pure ketone, and that they were the same enantiomer as the seeds. Thus, at the low supersaturation used, the seeding process was successful. Studies were also carried out at higher supersaturations, and these will be reported separately.

4. Solution Chemistry: Racemisation

In basic solution, the ketone will racemize (Fig 2). An attempt was made to study the rate of racemization using an optical polarimeter (Optical Activity AA 100). 2.5g of (R)-ketone was dissolved in 200ml of 9:1 v/v methanol/water. The initial optical rotation of the solution at 20°C (589nm) was -0.543°, giving a specific rotation of -44.1°.

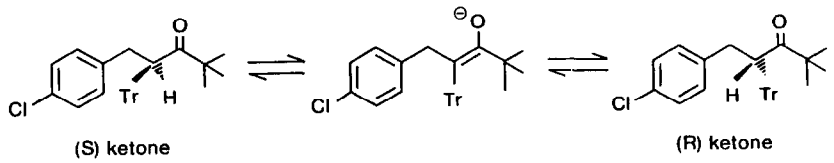

Fig 2. Racemisation of ketone.

Addition of 1% w/w sodium hydroxide resulted in racemization which was too rapid to measure. At a much lower concentration of base (0.001%), the observed optical rotation fell to half its initial value in 30 minutes. Thus the unwanted ketone enantiomer can be rapidly recycled to give racemic ketone, by the addition of base in methanol/water solution.

5. The Process.

It is possible to combine the seeded crystallisation and racemization steps into a single process, which has been called "crystallisation-induced asymmetric transformation"[4,5] (Fig. 3). Initially the solution is saturated with racemic ketone. Seed crystals of (S)-ketone are added and supersaturation is generated e.g. by cooling. The (S) crystals grow, creating an excess of (R)-ketone in solution. Rapid racemisation converts this excess into racemic ketone before (R)-ketone crystals can nucleate. As cooling continues, crystallisation and racemisation proceed simultaneously, so that in addition to crystallising (S)-ketone, (R)-ketone from solution is converted to solid (S)-ketone.

To ensure that the (R)-ketone does not nucleate, the crystallisation must be controlled so that the supersaturation is always low. Three different ways of achieving this were studied.

5.1 Cooling.

The solubility of (RS)-ketone in 3:1 w/w methanol/water is strongly dependent on temperature; decreasing from 4.3% w/w at 30°C to 3.3% w/w at 24.5°C. Therefore, provided the temperature control is adequate and the cooling rate sufficiently slow, a seeded separation should be possible.

1% w/w sodium hydroxide was dissolved in 3:1 w/w methanol/water, and the solution was saturated with (RS) ketone at 30°C. 0.04% w/w of (R)-ketone seeds were added to the solution, which was cooled at 1°C per hour until a final temperature of 24.5°C was reached. The solution was filtered and the solids washed with slightly acidified 1:1 w/w methanol/water. The theoretical yield, based on the solubility curve, is 1.0% w/w; the yield obtained here was 0.83% w/w. The enantiomeric purity, as determined by HPLC, was 99%.

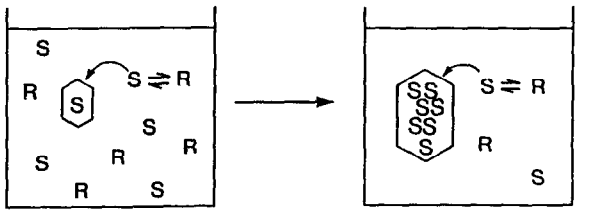

Fig 3. Process Scheme

5.2 Controlled evaporation

A saturated solution of (RS)-ketone in 500g methanol containing 1% w/w sodium hydroxide at 39.8°C was prepared. 3g of S-ketone seeds were added, and 39g of solvent were removed by distillation under a reduced pressure of 240mm Hg over 37 minutes, whilst the temperature was maintained at at 39.5±0.5°C. The product was isolated as above. 9.6g of product were obtained with an optical purity (by HPLC) of 96.8%.

5.3 Drown-out

(RS)-ketone is almost completely insoluble in water, and highly soluble in methanol, so controlled addition of water provides a third route to generating low supersaturation. 400g of 3:1 w/w methanol/water containing 1% w/w sodium hydroxide was saturated with (RS)-ketone at 49.8°C. 0.004g seeds of (R)-ketone were added, followed by 440g of water at the same temperature as the saturated solution, at 0.25g/minute. The product was isolated as above, giving a yield of 29g which had an enantiomeric purity of 96.9%.

6. Discussion

The successful development of this process has necessitated an appreciation of the organic, solution and crystal chemistry. The seeding process described is only successful because firstly the ketone crystallises as a racemic mixture; secondly the base-catalysed racemisation is rapid, and thirdly stereospecific reduction to the desired product is possible.

The ease of operation of this method makes it an extremely attractive option for preparing enantiomerically pure paclobutrazol. To apply this method to a different system, it is first necessary to understand the crystal chemistry of that system. If, for example, as in many cases, crystallisation from racemic solutions yields racemic crystals, then the method will not work. In such cases, the crystal chemistry of simple derivatives (e.g. solvates) or other intermediates may be favourable.

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Appendix.

HPLC Method

All analyses were carried out using a CHIRALCEL OC column supplied by Diacel Chemical Industries Ltd. Other conditions were:

Solvent:	Hexane/Absolute Alcohol 95/5 v/v
Detector Wavelength:	230nm
Flow Rate:	1.5ml/min.
Temperature:	Ambient