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SYNTHESIS OF OPTICALLY ACTIVE CYANOHYDRINS USING ALMOND MEAL.

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abstract: Asymmetric hydrocyanation of aldehydes was accomplished using almond meal, containing the enzyme oxynitrilase. Optically active cyanohydrins with high levels of enantiomeric purity were obtained following a simple procedure.

Asymmetric hydrocyanation of aldehydes has been a topic of great interest in the past decade. The products of these reactions, optically active cyanohydrins, are key intermediates in the synthesis of several important classes of chiral compounds, such as α-hydroxy acids[1], acyloins[2] and ß-amino alcohols[3,4]. Optically active cyanohydrins can be prepared using chiral catalysts[5-7] or the enzyme oxynitrilase (E.C. 4.1.2.10 and E.C. 4.1.2.11). The enzyme catalyzed reaction has thusfar been reported with crude extracts from almond meal[2] and with purified oxynitrilases from sorghum[8] and almonds[9]. The latter procedure uses oxynitrilase supported on cellulose and ethyl acetate as the solvent. Drawbacks of this method are the need to have

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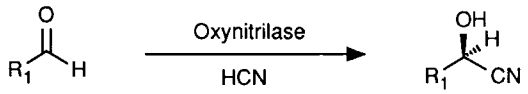
the disposal of purified enzyme and the use of free hydrocyanic acid (HCN). We wish to report a new enzymatic method for the asymmetric hydrocyanation of aldehydes. The method is similar to the cellulose method, but does not suffer from drawbacks mentioned earlier.

Almond meal itself was found to be not only a convenient source of the enzyme but at the same time a suitable enzyme supporting material and can therefore be used in a exceedingly simple procedure for the synthesis of optically active cyanohydrins. There is no need to purify the enzyme and the use of free hydrocyanic acid is circumvented by preparing a ethyl acetate solution in situ. The almond meal system was tested on five aldehydes (**1a-e**) which were known to be substrates for the enzyme[10]. The results are presented in Table 1.



aldehyde **1a** benzaldehyde
1b 4-(MeO)benzaldehyde
1c 5-(Me)furfuraldehyde
1d butyraldehyde
1e crotonaldehyde

cyanohydrin **2(a-e)**

A general procedure for enzymatic HCN addition to aldehydes is as follows:

(*R*)-Mandelonitrile (2a): In a 250 mL round bottom flask three grams of almond meal[11] was swollen with 4.5 mL of a 0.02 M citrate buffer pH = 5.5 for 15 min. A solution of freshly distilled benzaldehyde (**1a**, 20 mmol, 2.12 g) in 5 mL of ethyl acetate was added. To the magnetically stirred

Table 1: Optically active cyanohydrins from aldehydes using almond meal.

aldehyde	time (hours)	temp. (°C)	conv. (%)	cyanohydrin	recovery (%)	e.e. (%)
1a	16	4	100	**(*R*)-2a**	98	99
1b	89	20	47	**(*R*)-2b**	100	99
1c	17	4	70	**(*S*)-2c**[13]	100	99
1d	41	4	100	**(*R*)-2d**	95	89
1e	41	4	100	**(*R*)-2e**	73	99

suspension, 1.5 eq HCN in ethyl acetate[12] (75 mL) was added and stirring was continued overnight at 4 °C. The reaction mixture was then filtered through a glass filter and the residue was washed twice with ethyl acetate. The filtrate was dried over Na_2SO_4 and concentrated in vacuo to leave a yellow oil (2.60 g, 98%) with analytical data in complete agreement with literature reports[2,10].

References and Notes

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11. Almond meal is commercially available from the Sigma Chemical Company. The material used in the experiments described here was prepared by grinding almonds and defatting three times with ethyl acetate.

12. To avoid the use of free HCN and to saturate ethyl acetate with an acetate buffer pH = 5.5 the following procedure was followed: NaCN (2.1 g, 43 mmol) was dissolved in water (75 mL). Acetic acid was added until pH = 5.5. The HCN was then extracted with ethyl acetate (75 mL). The amount of HCN in the organic phase was determined by a slightly modified literature procedure[14]; 1.0 mL of the organic phase was diluted with 20 mL of water and 5 mL of a whirling $Mg(OH)_2$ suspension in water and titrated with 0.1 N $AgNO_3$ using K_2CrO_4 as indicator.

13. The cyanohydrins possess a similar spatial arrangement. Due to priority rules cyanohydrin **2c** must be assigned the (*S*)-configuration.

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