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Enzymatic Alkylation of α-Cyanoketones by Bakers Yeast

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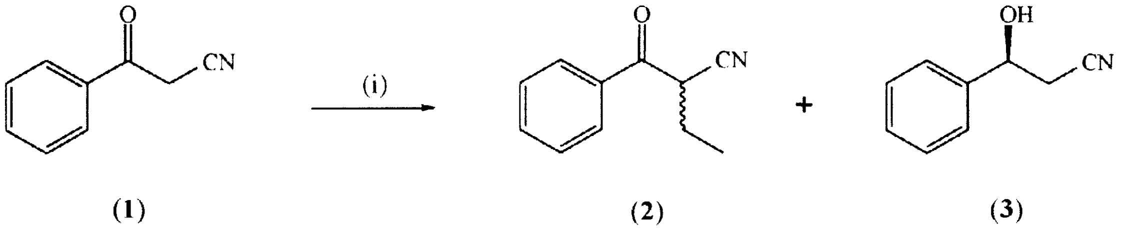
Abstract: In an organic solvent system, 3-oxo-3-arylpropanenitriles are C-alkylated by bakers yeast. The reported mechanism for bakers yeast alkylation of ethyl cyanoacetate (**13**), in an aqueous system, has been revised. © 1998 Elsevier Science Ltd. All rights reserved.

The use of bakers yeast as a reagent in organic synthesis has been well documented.[1,2] In recent times, the incorporation of an organic solvent system has extended the utility of this reagent in providing improvements in isolated yield and, more importantly, greater enantioselectivity.[3]

In our screening for aromatic ketones which may be amenable to bakers yeast reduction, the major product obtained from the reaction of 3-oxo-3-phenylpropanenitrile (**1**) with bakers yeast was 2-cyano-1-phenylbutanone (**2**) (Scheme 1). Thus the addition of bakers yeast (25 g) to a stirred suspension of 3-oxo-3-phenylpropanenitrile (**1**) (5 mmol) and water (20 ml) in petrol (40-60) (200 ml) gave, after stirring for 24 h at room temperature and subsequent extraction (CH_2Cl_2) and flash chromatography of the residue (gradient elution with ether/petrol 40-60), 2-cyano-1-phenylbutanone (**2**) (40 %) as a racemate and (*S*)-3-hydroxy-3-phenylpropanenitrile (**3**) in low yield (10 %).



Scheme 1: (i) bakers yeast, H_2O, petrol 40-60

During optimisation studies, the addition of 2 equivalents of acetaldehyde to the reaction mixture gave exclusive formation of 2-cyano-1-phenylbutanone (**2**) in good yield (71 %). Using this general procedure, the scope of the reaction was investigated in a number of substituted aromatic compounds (Scheme 2).[4] Thus 3-oxo-3-(3'-methyl)phenylpropanenitrile (**4**) gave the alkylated product (**5**) in 75% yield. Similarly the methoxy substituted derivatives (**6**) and (**8**) gave the corresponding alkylated products (7) and (**9**) in moderate yield.

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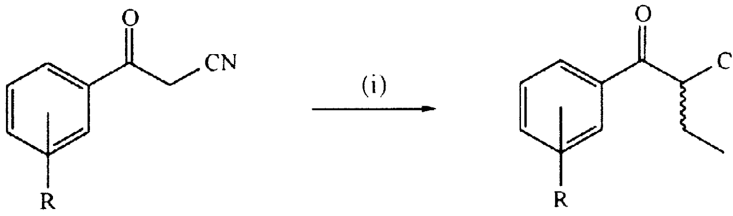
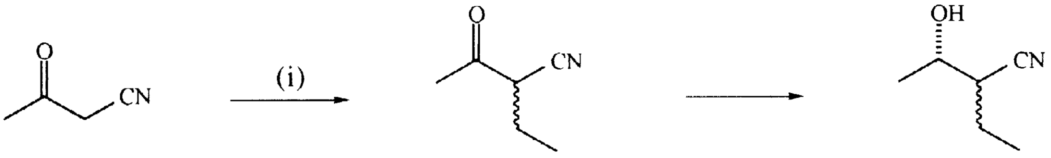


		Yield (%)
(**1**) R = H	(**2**) R = H	71
(**4**) R = 3-Me	(**5**) R = 3-Me	75
(**6**) R = 2-OMe	(**7**) R = 2-OMe	60
(**8**) R = 3-OMe	(**9**) R = 3-OMe	59

Scheme 2: (i) bakers yeast, acetaldehyde, H_2O, petrol 40-60

In an earlier report by Itoh *et. al.*,[5] the reaction of 3-oxobutyronitrile (**10**) with bakers yeast was found to give (3S)-2-ethyl-3-hydroxybutyronitrile (**12**) in high yield. The ketone (**11**) was isolated in 58 % yield using a shorter reaction time.



(**10**) (**11**) (**12**)

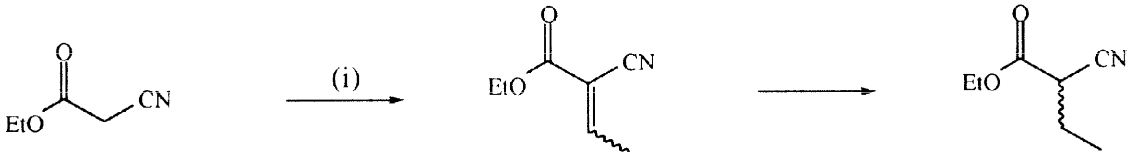
Scheme 3: (i) bakers yeast, glucose, H_2O

Subsequently Fuganti and co-workers[6] investigated the mechanism of the alkylation reaction and using ethyl cyanoacetate (**13**) as a substrate, the authors proposed a mechanism for the reaction which involved;

a) yeast oxidation of added ethanol to acetaldehyde.

b) condensation with the active methylene group of the nitrile.

c) double bond reduction by yeast to give the saturated product (**15**).



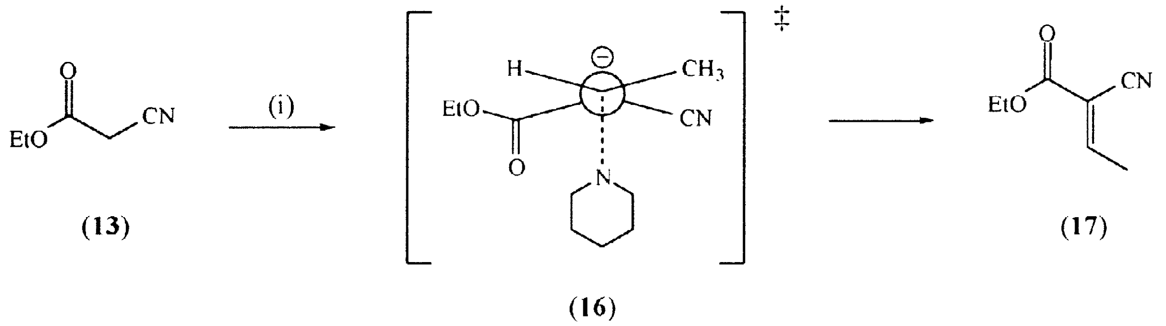
(**13**) (**14**) (**15**)

Scheme 4: (i) bakers yeast, EtOH, H_2O (product not isolated)

The authors also reported that double bond formation in (**14**) was not stereoselective and attributed this result as a probable cause for the formation of a racemic product (Scheme 4). Notably, the basis of this report included comparison of gas chromatographic traces with material from the reaction of ethyl cyanoacetate with acetaldehyde at pH = 8 which the authors claimed to give a mixture of *E* and *Z* isomers.

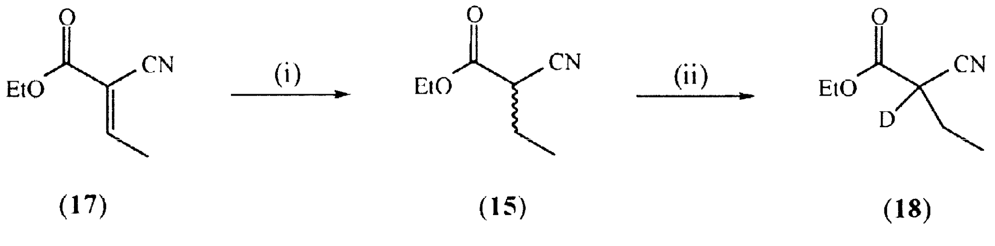
Revision of mechanism

In our hands the reaction of ethyl cyanoacetate (**13**) with acetaldehyde at pH = 8 (Na_2HPO_4) for 24 h gave a single geometric isomer (57 % yield). The GC trace and in particular, ^{1}H-nmr spectrum of the isolated product clearly showed that only one geometric isomer was formed.[7] The measurement of long range ^{13}C-^{1}H coupling constants in the coupled ^{13}C-nmr spectrum revealed that the product is the *E* isomer ($^3J_{CN-H}$ = 14 Hz) (**17**). A comparable yield of (*E*)-2-cyano-2-but-2-enoate (**17**) was obtained using conventional Knoevenagel reaction conditions.[8,9] Presumably the transition state (**16**) leading to the *E* product (E1cB mechanism) is favoured in order to avoid steric hindrance between the two larger substituents (Scheme 5).



Scheme 5: (i) acetaldehyde, piperidine/acetic acid

Reaction of the pure *E* isomer (**17**) (5 mmol) with bakers yeast (10 gm) in water (8 ml) and petrol 40-60 (150 ml) for 24 h gave ethyl 2-cyanobutanoate (**15**) (70 % yield) as a racemate. When the product (**15**) was subjected to the same reaction conditions with D_2O in place of H_2O, the incorporation of deuterium was implicated in the ^{1}H-nmr spectrum which showed a significant reduction in the intensity of the signal due to the H-2 proton. The mass spectrum gave a peak at *m/z* 142 which is consistent with the molecular formula $C_7H_{10}DNO_2$ for (**18**). Thus the most plausible explanation for the formation of a racemate in this instance is via exchange of the labile acidic proton at C-2 with the reaction medium.



Scheme 6: (i) bakers yeast, H_2O, petrol 40-60 (ii) bakers yeast, D_2O, petrol 40-60

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References and Notes

1. Csuk, R., Glänzer, B. I., *Chem. Rev.* 1991, **91**, 49.

2. Servi, S., *Synthesis*, 1990, 1.

3. Medson, C., Smallridge, A. J., Trewhella, M. A., *Tetrahedron: Asymmetry*, 1997, **8**, 1049 and references cited therin.

4. The α-cyanoketones were prepared using the procedure of Dorsch, J., and McElvain, S. M., *J. Am. Chem. Soc.*, 1932, **54**, 2960.

5. Itoh, T., Takagi, Y., and Fujisawa, T., *Tetrahedron Letters*, 1989, **30**, 3811.

6. Fuganti, C., Pedrocchi-Fantoni, G., Servi, S., *Tetrahedron Letters*, 1990, **31**, 4195.

7. A mixture of ethyl cyanoacetate (**13**) (3.18 g, 28 mmol), acetaldehyde (1.26 g, 28 mmol) and Na_2HPO_4 (80 mg, 0.56 mmol) in H_2O (40 ml) (initial pH = 8) was stirred at room temperature for 24 h. The mixture was diluted with saturated sodium chloride (40 ml) and extracted with dichloromethane (3 x 60 ml). The extracts were combined, dried (Na_2SO_4) and evaporated. The residue was subjected to flash-pad chromatography (ether/petrol 40-60 gradient elution) and subsequent distillation gave (*E*)-2-cyano-2-but-2-enoate (**17**) as a colourless oil (2.20 g, 57 %) b.p. 115 ^{0}C/20 mmHg (lit[9]. b.p. 71-72 ^{0}C/2.4 mmHg). ^{1}H-nmr (300 MHz) $\delta(CDCl_3)$ 1.35, (3H, t, *J* 7.1 Hz, $OCH_2\mathbf{CH_3}$), 2.25, (3H, d, *J* 7.2 Hz, H4), 4.31, (2H, q, *J* 7.1 Hz, $O\mathbf{CH_2}CH_3$), 7.72, (1H, q, *J* 7.2 Hz, H3).

8. These results are in full agreement with a previous publication which showed that under conventional Knoevenagel reaction conditions, the reaction of ethyl cyanoacetate (**13**) with acetaldehyde using piperidine/acetic acid as the catalyst gave ethyl (*E*)-2-cyanobut-2-enoate (**17**) exclusively; Yamamoto, Y. and Nishii, S., *J. Org. Chem.*, 1988, **53**, 3597.

9. Popp, F. D., and Catala, A., *J. Org. Chem.*, 1961, **26**, 2738.