A simple synthesis of (E)-3-formylbut-2-enenitrile, and its use as a precursor of isotope-labelled zeatin and (±)dihydrozeatin.

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Summary. (E)-3-Formylbut-2-enenitrile (4) is synthesized in 2 steps by reacting pyruvaldehyde dimethylacetal and acetonitrile in the presence of sodium methoxide, followed by acid hydrolysis to give 58% overall yield on distillation. The aldehyde 4 can be stepwise and selectively reduced to (E)-3-hydroxymethylbut-2-enylamine (7a) in 37% total yield or exhaustively reduced in 1 step to (±)-4-hydroxy-3-methylbutylamine (6) in 46% total yield. Compound 7a and 6 can be condensed with 6-chloropurine to give zeatin and (±)dihydrozeatin respectively. This provides a readily accessible method for isotope-labelled zeatin and its derivatives at side chain.

Zeatin (1) and dihydrozeatin (2) are highly active naturally occurring plant hormones which induce cell divisions in tissue culture. Synthesis of zeatin is of continuing interest to both organic and agricultural chemists because of the difficult problem in the construction of the small, but highly functionalized, key intermediate 7a and also because of the potential importance of the plant hormone in agricultural and biological research. Previous syntheses of 7a involve many steps, provide low yields and require the difficult separation of the geometric isomers. This latter problem has been diminished by a method reported by Ohsugi et al. We now report a novel and efficient synthesis of (E)-3-formylbut-2-enenitrile (4), which can be selectively or exhaustively reduced to 7a or 6. Compounds 7a and 6 can be condensed with 6-chloropurine to give zeatin and (±)dihydrozeatin respectively. Our method not only compares with that of Ohsugi et al. in the overall yield, but also provides a versatile process for the syntheses of isotope-labelled zeatin and its derivatives. We believe that the regiospecific synthesis of the highly functionalized isoprenoid compound 4 and the underlying reactions may also have wider synthetic implications.

We have found that whereas a methyl ketone such as acetophenone cannot be satisfactorily condensed with acetonitrile, an acetal of pyruvaldehyde, in which the α,β-dialkoxy substituent has a stabilizing effect on the polarizing carbonyl group, can be condensed with acetonitrile with surprisingly good results (65-75% isolated yield). Thus, pyruvaldehyde dimethylacetal is condensed with a large excess of acetonitrile in the presence of a strong base (1 mole equiv of NaOCH₃, reflux under nitrogen for 8 h) to give an isomeric mixture of the corresponding acetyl of 3-
formylbut-2-enenitrile 3 (b.p. 32-41°/0.2 mm, 70% isolated yield) with predominantly E-configuration (E/Z = 88/12). Hydrolysis of above isomeric acetal mixture 3 (0.5 N methanolic HCl solution) and distillation yielded exclusively the E-isomer of the α,β-unsaturated aldehyde (4) in a pure state (83% yield), eliminating the need for separating geometrical isomers at any point in the overall synthetic pathway. Presumably, the corresponding Z-isomer, further reacts intra- or intermolecularly to form a higher boiling fraction.

Compound 4 has the following physical parameters: b.p. 71°/11 mm; NMR (60 Hz, CDCl₃) δ 9.73 (s, 1H), 6.40 (q, J = 1.5 Hz, 1H), 2.10 (d, J = 1.5 Hz, 3H); IR (film) 2730 (vCH of CHO group), 2220 (vC=N) and 1705 cm⁻¹ (vC=O of α,β-unsaturated aldehyde); 2,4-DNPH, m.p. 276°C. The liquid aldehyde and the hydrazine gave correct elemental analysis and mass spectral data (M⁺ = 95 and 275 respectively).

Attempts to convert aldehyde 4 to the required unsaturated amino-alcohol 7a in 1 step by means of selective hydride reduction or catalytic hydrogenation were not successful. Attempts to convert aldehyde 4 to the required unsaturated pathway. Presumably, the corresponding Z-isomer, further reacts intra- or intermolecularly to form a higher boiling fraction.

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