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SYNTHESIS OF α-AMINOKETONES VIA SELECTIVE REDUCTION OF ACYL CYANIDES

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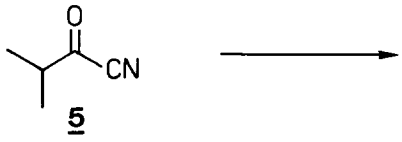
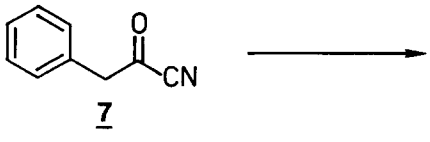
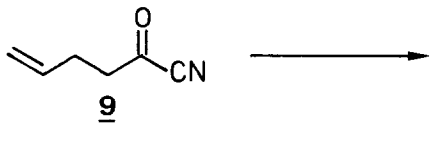
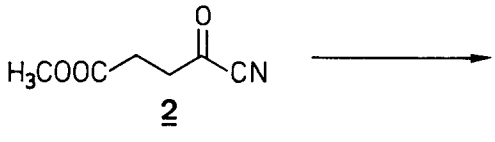
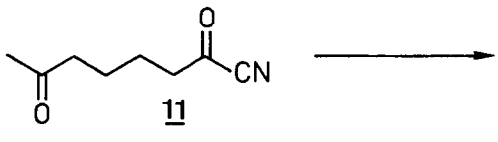
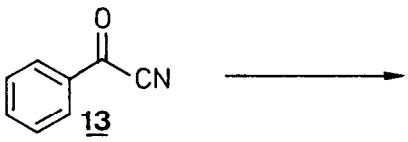
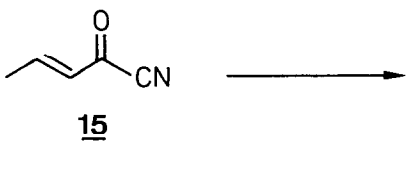
Abstract: Reduction of acyl cyanides with zinc in acetic acid in the presence of excess acetic anhydride leads to N-acetyl-α-aminoketones in good yields. An efficient three-step synthesis of 5-aminolevulinic acid by this method is described.

α-Aminoketones are versatile difunctional compounds. They have found a wide range of applications in organic synthesis, e.g. as building blocks for nitrogen-containing heterocycles.[1] We report here an efficient procedure for the preparation of α-aminoketones from carboxylic acids, based on the selective reduction of acyl cyanides.

In connection with the synthesis of ^{13}C-labelled 5-aminolevulinic acid 4 we have studied the reduction of methyl succinyl cyanide 2. Compound 2 would be an ideal, readily available precursor of 4, provided that the nitrile group could be selectively transformed to a primary amine without affecting the keto and ester groups. Starting from labelled cyanide or from labelled succinate, isotope labels could be easily introduced by this route, which would be of interest considering the numerous applications of ^{13}C-labelled 5-aminolevulinic acids in biochemical and structural studies of natural porphyrins and corrins.[2]

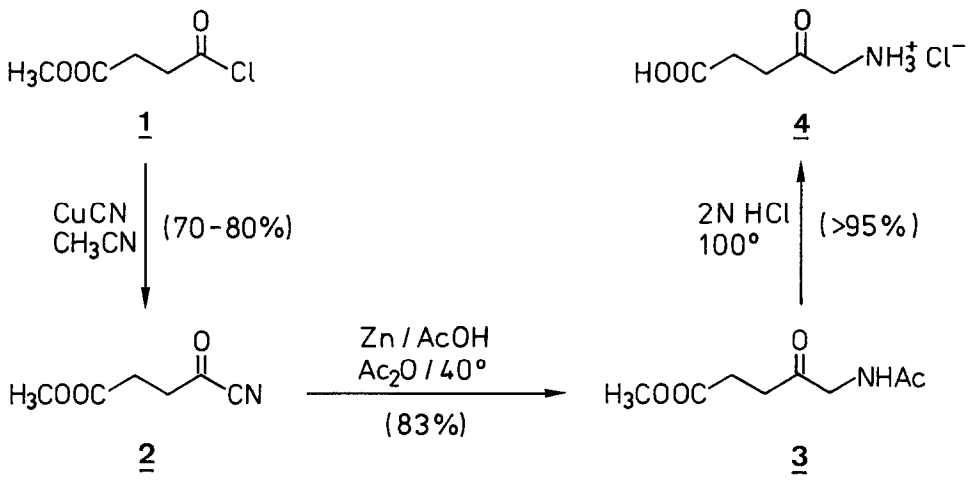
An example of conversion of an acyl cyanide to an α-aminoketone has been reported by Stuckwisch[3], who studied the Stephen reduction ($SnCl_2$/HCl) of aroyl cyanides leading to the corresponding amino-acetophenones. Our experiments with methyl succinyl cyanide 2 showed that an analogous transformation is also feasible in the aliphatic series. We found that compound 2 is cleanly reduced at the nitrile group with zinc in acetic acid in the presence of excess acetic anhydride.[4] Concomitant acetylation leads to the relatively stable N-acetyl derivative 3 of 5-aminolevulinic acid methyl ester, obtained as a crystalline compound in high yield.[5] Subsequent hydrolysis in aqueous hydrochloric acid affords the free amino acid, which can be isolated as the hydrochloride 4 in essentially quantitative yield (cf. Scheme 1). This route allows a convenient three-step preparation of 5-aminolevulinic acid 4 from commercially available methyl succinyl chloride 1 in ca. 60 % overall yield.[6] Our synthesis is particularly well suited to the introduction of a ^{13}C-label at C-5 starting from relatively inexpensive [^{13}C]-sodium cyanide.[7]

Table 1. Reduction of Acyl Cyanides with Zinc in Acetic Acid / Acetic Anhydride[12]

Entry	Reaction[a]	Yield[b]
(1)		75 %
(2)		71 %
(3)		74 %
(4)		83 %
(5)		70 %
(6)		(~30%)[c]
(7)		(~20%)[c] (~10%)[c]

[a]All reactions were done at 40 °C as described in the experimental procedure for the reduction of methyl succinyl cyanide 2.[12] The acyl cyanides were prepared from the corresponding acyl chlorides and CuCN[10] or Me_3SiCN[9,11]. [b]Yields of spectroscopically pure products after chromatography and recrystallization. [c]Approximate yields of chromatographed (non-crystalline) products obtained in preliminary experiments.

Scheme 1



To evaluate the scope of the method, we have treated various types of acyl cyanides with zinc in acetic acid / acetic anhydride. The results are summarized in Table 1. With the exception of aromatic and α,β-unsaturated acyl cyanides the method seems to be generally applicable, and the corresponding N-acetyl-α-aminoketones are obtained in good yields. The reagent is mild and selective; C=C double bonds like the vinyl group in 9, as well as ester and keto functions are not affected under the reaction conditions (cf. entries 3, 4 and 5).

In the case of the α,β-unsaturated acyl cyanide 15, not unexpectedly, the reaction took a different course (entry 7). In addition to the usual transformation of the nitrile to an acetamido-methyl group a non-specific reduction of the enone system at either the C=C or the C=O double bond was observed. Zinc reduction of benzoyl cyanide did not lead to the corresponding acetamido-ketone (entry 6); the only product, isolated in low yield, was the cyanohydrin of benzaldehyde.[8]

In recent years a number of efficient methods for the preparation of acyl cyanides have been developed.[9] The most general routes start from the corresponding carboxylic acids and involve the reaction of an acyl halide with cuprous cyanide[10] or trimethylsilyl cyanide[9,11]. The reduction of acyl cyanides described here can thus be considered an attractive alternative to established methods[1,6] for the synthesis of aminomethyl-ketones.

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References and Notes

1. D. Mayer in "Houben-Weyl, Methoden der Organischen Chemie", 4th. Ed., Vol. 7/2c, p. 2251 (Thieme, Stuttgart 1977).
2. See e.g.: A.I. Scott, Pure Appl. Chem. 53, 1215 (1981); A.R. Battersby, E. McDonald in "B_{12}", D. Dolphin Ed., Vol. 1, p. 107 (Wiley, New York 1982); A. Pfaltz, B. Jaun, A. Fässler, A. Eschenmoser; R. Jaenchen, H.H. Gilles, G. Diekert, R.K. Thauer, Helv. Chim. Acta 65, 828 (1982).
3. C.G. Stuckwisch, J. Org. Chem. 37, 318 (1972). According to a patent α-amino-acetophenones can also be prepared by catalytic hydrogenation of aroyl cyanides (H. Brachwitz, K.H. Werner, DDR-Pat. 65929 (1969); C.A. 71, 123965s (1969); cf. reference 1, p. 2516).
4. The reduction has to be done in the presence of a large excess of acetic anhydride in order to prevent amide formation between the resulting aminoketone and the acyl cyanide.
5. Catalytic hydrogenation of methyl succinyl cyanide 2 (Pd-C; 1 atm. H_2; AcOH/Ac_2O) gave the same product 3 albeit in lower and less reproducible yield (40 - 65 %).
6. For other syntheses of 5-aminolevulinic acid cf.: D.A. Evans, P.J. Sidebottom, J. Chem. Soc. Chem. Commun. 1978, 753; G. Schulz, W. Steglich, Chem. Ber. 113, 787 (1980) and the review of R.B. Frydman, B. Frydman & A. Valasinas in "The Porphyrins", D. Dolphin Ed., Vol. VI, Part A, p. 12 (Academic Press, New York 1979).
7. A. Pfaltz, A. Fässler, Helv. Chim. Acta (in preparation).
8. In contrast to the results obtained with Zn/AcOH/Ac_2O, benzoyl cyanide is converted to α-amino-acetophenone in 67 % yield by reduction with $SnCl_2$/HCl.[3]
9. S. Hünig, R. Schaller, Angew. Chem. 94, 1 (1982); Angew. Chem., Int. Ed. 21, 36 (1982).
10. J.F. Normant, C. Piechucki, Bull. Soc. Chim. Fr. 1972, 2402.
11. K. Herrmann, G. Simchen, Synthesis 1979, 204; U. Hertenstein, S. Hünig, H. Reichelt, R. Schaller, Chem. Ber. 115, 261 (1982).
12. Experimental Procedure: A solution of methyl succinyl cyanide 2 (3.0 g, 21 mmol) in acetic acid (4 ml) / acetic anhydride (4 ml) was added dropwise to a suspension of activated zinc dust (12 g) in acetic acid (30 ml) / acetic anhydride (30 ml) under nitrogen. During the addition, which took ca. 10 min, the temperature was kept at 40 °C. After stirring for additional 90 min at 40 °C, the reaction mixture was cooled to room temperature and filtered. The remaining solid was washed with methylene chloride. The solvents were removed at 0.01 torr. Flash chromatography on a 3 x 15 cm silica gel column (EtOAc/MeOH 10:1) afforded a yellowish oil (R_f = 0.31), which solidified upon drying at 0.01 torr. Recrystallization from toluene gave 3.3 g (83 %) of acetamido-ketone 3 as a white crystalline solid (mp. 52 - 53 °C).

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